

Report

Epigenetic & Environment-Epigenetica ed ambiente

Barbara Federica Scremin ^{1*}

¹ CNR, National Research Council of Italy, IOM-Materials Foundry Institute, Area Science Park-Basovizza, Strada Satale 14, km 163.5, 34149 Trieste, Italy.

* Correspondence: scremin@iom.cnr.it; Tel.: +39 3282097825

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epigenetica

Studio delle modifiche chimiche, a carico del DNA o delle regioni che lo circondano, che non coinvolgono cambiamenti nella sequenza dei nucleotidi. Tali modifiche regolano l'accesso dei fattori di trascrizione ai loro siti di legame sul DNA e regolano in modo diretto lo stato di attivazione funzionale dei geni. Poiché l'esperienza ambientale modula i livelli e la natura dei segnali epigenetici, essi sono considerati fondamentali nel mediare la capacità dell'ambiente di regolare il genoma. L'e. svolge un ruolo fondamentale in tutti i processi di riorganizzazione o ristrutturazione neurale, compresi quelli che presiedono alla plasticità cerebrale. (per lo più tramite le emozioni mediate dai neuroni specchio).

epigenetics

The study of chemical modifications to DNA or the regions surrounding it that do not involve changes in the nucleotide sequence. These modifications regulate the access of transcription factors to their binding sites on DNA and directly regulate the functional activation state of genes. Since environmental experience modulates the levels and nature of epigenetic signals (protein expression), they are considered essential in mediating the ability of the environment to regulate the genome.

E. plays a fundamental role in all processes of neural reorganization or restructuring, including those that govern brain plasticity. (I think mostly by emotions and mirror neurons)

[https://www.treccani.it/enciclopedia/epigenetica_\(Dizionario-di-Medicina\)/](https://www.treccani.it/enciclopedia/epigenetica_(Dizionario-di-Medicina)/)

+myself

Questo significa che un DNA alterato, può funzionare in maniera normale. Il Cancro è indotto da un DNA danneggiato, per esempio. L'alimentazione è anche in grado di modulare l'espressione proteica del DNA. Ma non solo è tutto l'ambiente in cui gli esseri viventi sono inseriti che incide sul funzionamento del DNA.

This means that an altered DNA can function normally. Cancer is induced by damaged DNA, for example. Nutrition is also able to modulate the protein expression of DNA. But it is not only the entire environment in which living beings are inserted that affects the functioning of DNA.

epigenetica«e·pi·ge·nè·ti·ca» s.f. ~ Branca della biologia molecolare che studia le mutazioni genetiche e la trasmissione di caratteri ereditari non attribuibili direttamente alla sequenza del DNA. ETIMOLOGIA Der. di genetica, col pref. epi-DATA 1965. The Greek prefix epi- (ἐπι- "over, outside of, around") in epigenetics implies features that are "on top of" or "in addition to" the traditional (DNA sequence based) genetic mechanism of inheritance.

Author considerations

Tutto ciò che concerne l'ambiente in cui i viventi esistono, incluso il bagaglio interiore, spirituale è in grado di modulare le funzioni geniche, perché questo è in grado di modulare l'interazione con l'ambiente stesso. Siamo esseri interiori ed esternalizzati. Abbiamo una responsabilità sulla stessa prole, perché anche il cancro ha una componente ereditaria, e se il cancro danneggia il DNA, che viene poi trasmesso alla prole, io credo che anche le espressioni geniche-emozioni dei genitori vengano a "nutrire" il feto. Le donne hanno bisogno di sentirsi protette dal compagno durante la maternità in particolar modo, perché le emozioni contano.

Everything that concerns the environment in which living beings exist, including the internal, spiritual baggage is able to modulate the gene functions, because this is able to modulate the interaction with the environment itself. We are internal and externalized beings. We have a responsibility for the offspring itself, because cancer also has a hereditary component, and if cancer damages the DNA, which is then transmitted to the offspring, I believe that the parents' gene-emotion expressions also come to "nourish" the fetus. Women need to feel protected by their partner during maternity in particular, because emotions matter.

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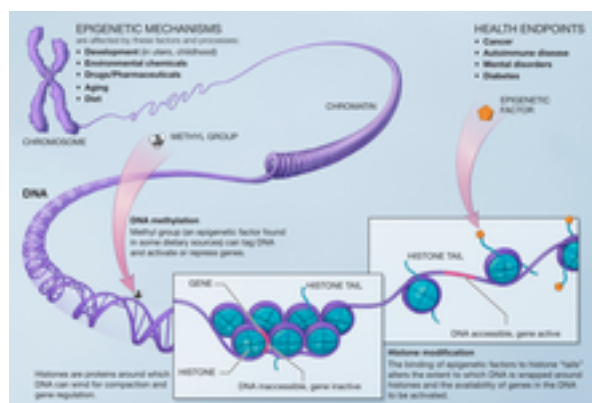
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For other uses, see [Epigenetic \(disambiguation\)](#).



Epigenetic mechanisms

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In [biology](#), **epigenetics** is the study of [heritable traits](#), or a stable change of cell function, that happen without changes to the [DNA sequence](#).^[1] The [Greek](#) prefix *epi-* (ἐπι- "over, outside of, around") in *epigenetics* implies features that are "on top of" or "in addition to" the traditional (DNA sequence based) [genetic](#) mechanism of inheritance.^[2] Epigenetics usually involves a change that is not erased by cell division, and affects the [regulation of gene expression](#).^[3] Such effects on [cellular](#) and [physiological phenotypic traits](#) may result from [environmental](#) factors, or be part of normal development. Epigenetic factors can also lead to cancer.^[4]

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The term also refers to the mechanism of changes: functionally relevant alterations to the [genome](#) that do not involve mutation of the [nucleotide sequence](#). Examples of mechanisms that produce such changes are [DNA methylation](#) and [histone modification](#), each of which alters how genes are expressed without altering the underlying [DNA](#) sequence.^[5] Further, non-coding RNA sequences have been shown to play a key role in the regulation of gene expression.^[6] Gene expression can be controlled through the action of [repressor proteins](#) that attach to [silencer](#) regions of the DNA. These epigenetic changes may last through [cell divisions](#) for the duration of the cell's life, and may also last for multiple generations, even though they do not involve changes in the underlying DNA sequence of the organism;^[7] instead, non-genetic factors cause the organism's genes to behave (or "express themselves") differently.^[8]

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One example of an epigenetic change in [eukaryotic](#) biology is the process of [cellular differentiation](#). During [morphogenesis](#), [totipotent stem cells](#) become the various [pluripotent cell lines](#) of the [embryo](#), which in turn become fully differentiated cells. In other words, as a single fertilized [egg cell](#) – the [zygote](#)– continues to [divide](#), the resulting daughter cells change into all the different cell types in an organism, including [neurons](#), [muscle cells](#), [epithelium](#), [endothelium](#) of [blood vessels](#), etc., by activating some genes while inhibiting the expression of others.^[9]

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Definitions

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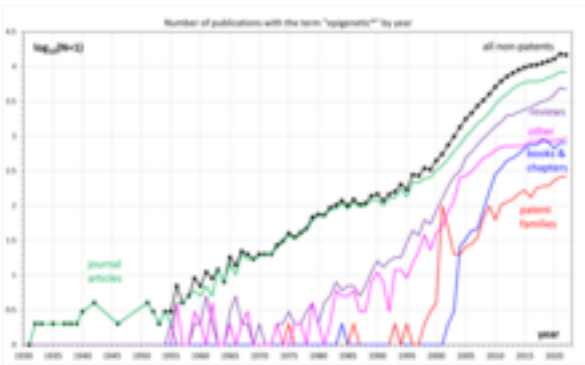
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The term *epigenesis* has a generic meaning of "extra growth" that has been used in English since the 17th century.^[10] In scientific publications, the term *epigenetics* started to appear in the 1930s (see Fig. on the right). However, its contemporary meaning emerged only in the 1990s.^[11]

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Number of patent families and non-patent documents with the term

"epigenetic*" by publication year

A definition of the concept of *epigenetic trait* as a "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" was formulated at a [Cold Spring Harbor](#) meeting in 2008,^[12] although alternate definitions that include non-heritable traits are still being used widely.^[13]

Waddington's canalisation, 1940s

[edit]

The hypothesis of epigenetic changes affecting the expression of [chromosomes](#) was put forth by the Russian biologist [Nikolai Koltsov](#).^[14] From the generic meaning, and the associated adjective *epigenetic*, British embryologist [C. H. Waddington](#) coined the term *epigenetics* in 1942 as pertaining to *epigenesis*, in parallel to [Valentin Haecker](#)'s 'phenogenetics' (*Phänogenetik*).^[15] *Epigenesis* in the context of the biology of that period referred to the [differentiation](#) of cells from their initial [totipotent](#) state during [embryonic development](#).^[16]

When Waddington coined the term, the physical nature of [genes](#) and their role in heredity was not known. He used it instead as a conceptual model of how genetic components might interact with their surroundings to produce a [phenotype](#); he used the phrase "[epigenetic landscape](#)" as a metaphor for [biological development](#). Waddington held that cell fates were established during development in a process he called [canalisation](#) much as a marble rolls down to the point of [lowest local elevation](#).^[17] Waddington suggested visualising increasing irreversibility of cell type differentiation as ridges rising between the valleys where the marbles (analogous to cells) are travelling.^[18]

In recent times, Waddington's notion of the epigenetic landscape has been rigorously formalized in the context of the [systems dynamics](#) state approach to the study of cell-fate.^{[19][20]} Cell-fate determination is predicted to exhibit certain dynamics, such as attractor-convergence (the attractor can be an equilibrium point, limit cycle or [strange attractor](#)) or oscillatory.^[20]

Contemporary

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In 1990, [Robin Holliday](#) defined epigenetics as "the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms."^[21]

More recent usage of the word in biology follows stricter definitions. As defined by [Arthur Riggs](#) and colleagues, it is "the study of [mitotically](#) and/or [meiotically](#) heritable changes in gene function that cannot be explained by changes in DNA sequence."^[22]

The term has also been used, however, to describe processes which have not been demonstrated to be heritable, such as some forms of histone modification. Consequently, there are attempts to redefine "epigenetics" in broader terms that would avoid the constraints of requiring [heritability](#). For example, [Adrian Bird](#) defined epigenetics as "the structural adaptation of chromosomal

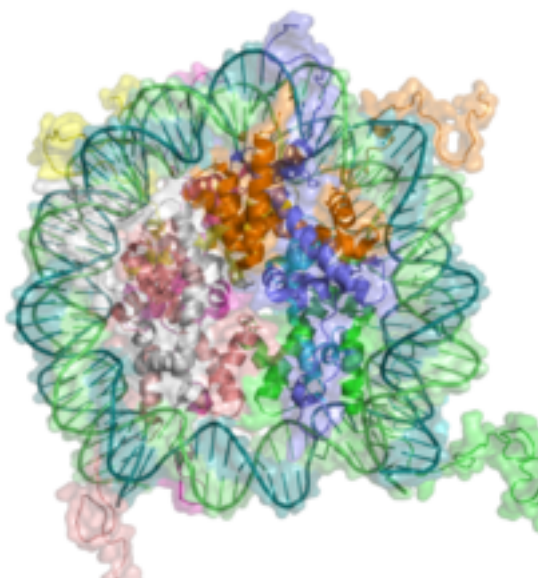
regions so as to register, signal or perpetuate altered activity states."^[2] This definition would be inclusive of transient modifications associated with [DNA repair](#) or [cell-cycle](#) phases as well as stable changes maintained across multiple cell generations, but exclude others such as templating of membrane architecture and [prions](#) unless they impinge on chromosome function. Such redefinitions however are not universally accepted and are still subject to debate.^[23] The [NIH](#) "Roadmap Epigenomics Project", which ran from 2008 to 2017, uses the following definition: "For purposes of this program, epigenetics refers to both heritable changes in gene activity and [expression](#) (in the progeny of cells or of individuals) and also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable."^[24] In 2008, a consensus definition of the epigenetic trait, a "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence," was made at a [Cold Spring Harbor](#) meeting.^[12]

The similarity of the word to "genetics" has generated many parallel usages. The "[epigenome](#)" is a parallel to the word "[genome](#)", referring to the overall epigenetic state of a cell, and [epigenomics](#) refers to global analyses of epigenetic changes across the entire genome.^[13] The phrase "[genetic code](#)" has also been adapted – the "[epigenetic code](#)" has been used to describe the set of epigenetic features that create different phenotypes in different cells from the same underlying DNA sequence. Taken to its extreme, the "epigenetic code" could represent the total state of the cell, with the position of each molecule accounted for in an *epigenomic map*, a diagrammatic representation of the gene expression, DNA methylation and histone modification status of a particular genomic region. More typically, the term is used in reference to systematic efforts to measure specific, relevant forms of epigenetic information such as the [histone code](#) or [DNA methylation](#) patterns.^[citation needed]

Mechanisms

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[Covalent](#) modification of either DNA (e.g. cytosine methylation and hydroxymethylation) or of histone proteins (e.g. lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, and lysine ubiquitination and sumoylation) play central roles in many types of epigenetic inheritance. Therefore, the word "epigenetics" is sometimes used as a synonym for these processes. However, this can be misleading. Chromatin remodeling is not always inherited, and not all epigenetic inheritance involves chromatin remodeling.^[25] In 2019, a further lysine modification appeared in the scientific literature linking epigenetics modification to cell metabolism, i.e. lactylation^[26]



DNA associates with histone proteins to form chromatin.

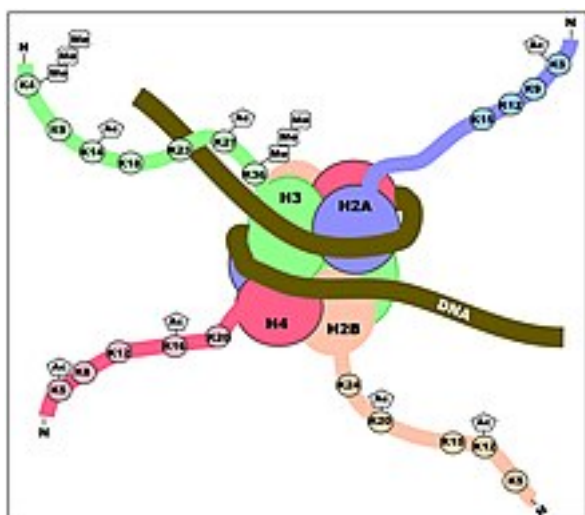
Because the [phenotype](#) of a cell or individual is affected by which of its genes are transcribed, heritable [transcription states](#) can give rise to epigenetic effects. There are several layers of regulation of [gene expression](#). One way that genes are regulated is

through the remodeling of chromatin. Chromatin is the complex of DNA and the [histone](#) proteins with which it associates. If the way that DNA is wrapped around the histones changes, gene expression can change as well. Chromatin remodeling is accomplished through two main mechanisms:

1. The first way is [post translational modification](#) of the amino acids that make up histone proteins. Histone proteins are made up of long chains of amino acids. If the amino acids that are in the chain are changed, the shape of the histone might be modified. DNA is not completely unwound during replication. It is possible, then, that the modified histones may be carried into each new copy of the DNA. Once there, these histones may act as templates, initiating the surrounding new histones to be shaped in the new manner. By altering the shape of the histones around them, these modified histones would ensure that a lineage-specific transcription program is maintained after cell division.
2. The second way is the addition of methyl groups to the DNA, mostly at [CpG sites](#), to convert [cytosine](#) to [5-methylcytosine](#). 5-Methylcytosine performs much like a regular cytosine, pairing with a guanine in double-stranded DNA. However, when methylated cytosines are present in [CpG sites](#) in the [promoter](#) and [enhancer](#) regions of genes, the genes are often repressed.^{[27][28]} When methylated cytosines are present in [CpG sites](#) in the gene body (in the [coding region](#) excluding the transcription start site) expression of the gene is often enhanced. Transcription of a gene usually depends on a [transcription factor](#) binding to a (10 base or less) [recognition sequence](#) at the enhancer that interacts with the promoter region of that gene ([Gene expression#Enhancers, transcription factors, mediator complex and DNA loops in mammalian transcription](#)).^[29] About 22% of transcription factors are inhibited from binding when the recognition sequence has a methylated cytosine. In addition, presence of methylated cytosines at a promoter region can attract [methyl-CpG-binding domain](#) (MBD) proteins. All MBDs interact with [nucleosome](#) remodeling and [histone deacetylase](#) complexes, which leads to gene silencing. In addition, another covalent modification involving methylated cytosine is its [demethylation](#) by [TET enzymes](#). Hundreds of such demethylations occur, for instance, during [learning and memory](#) forming events in [neurons](#).^{[30][31]}

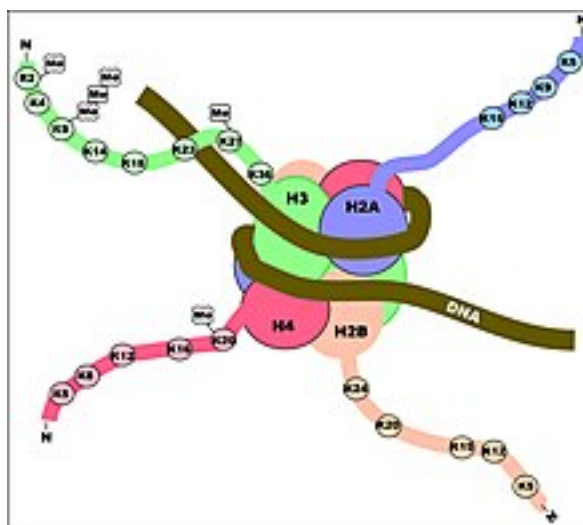
There is frequently a reciprocal relationship between DNA methylation and histone lysine methylation.^[32] For instance, the [methyl binding domain protein MBD1](#), attracted to and associating with [methylated cytosine](#) in a DNA [CpG site](#), can also associate with H3K9 [methyltransferase](#) activity to methylate histone 3 at lysine 9. On the other hand, DNA maintenance methylation by [DNMT1](#) appears to partly rely on recognition of histone methylation on the nucleosome present at the DNA site to carry out cytosine methylation on newly synthesized DNA.^[32] There is further crosstalk between DNA methylation carried out by [DNMT3A](#) and [DNMT3B](#) and histone methylation so that there is a correlation between the genome-wide distribution of DNA methylation and histone methylation.^[33]

Mechanisms of heritability of histone state are not well understood; however, much is known about the mechanism of heritability of DNA methylation state during cell division and differentiation. Heritability of methylation state depends on certain enzymes (such as [DNMT1](#)) that have a higher affinity for 5-methylcytosine than for cytosine. If this enzyme reaches a "hemimethylated" portion of DNA (where 5-methylcytosine is in only one of the two DNA strands) the enzyme will methylate the other half. However, it is now known that DNMT1 physically interacts with the protein [UHRF1](#). UHRF1 has been recently recognized as essential for DNMT1-mediated maintenance of DNA methylation. UHRF1 is the protein that specifically recognizes hemi-methylated DNA, therefore bringing DNMT1 to its substrate to maintain DNA methylation.^[33]



Some acetylations and some methylations of lysines (symbol K) are

activation signals for transcription when present on a [nucleosome](#), as shown in the top figure. Some methylations on lysines or arginine (R) are repression signals for transcription when present on a [nucleosome](#), as shown in the bottom figure. [Nucleosomes](#) consist of four pairs of [histone](#) proteins in a tightly assembled core region plus up to 30% of each histone remaining in a loosely organized tail^[34] (only one tail of each pair is shown). DNA is wrapped around the histone core proteins in [chromatin](#). The lysines (K) are designated with a number showing their position as, for instance (K4), indicating lysine as the 4th amino acid from the amino (N) end of the tail in the histone protein. [Methylations](#) [Me], and [acetylations](#) [Ac] are common [post-](#)



[translational modifications](#) on the lysines of the histone tails.

Although histone modifications occur throughout the entire sequence, the unstructured N-termini of histones (called histone tails) are particularly highly modified. These modifications include [acetylation](#), [methylation](#), [ubiquitylation](#), [phosphorylation](#), [sumoylation](#), ribosylation and citrullination. Acetylation is the most highly studied of these modifications. For example, acetylation of the K14 and K9 [lysines](#) of the tail of histone H3 by histone acetyltransferase enzymes (HATs) is generally related to transcriptional competence^[35] (see Figure).

One mode of thinking is that this tendency of acetylation to be associated with "active" transcription is biophysical in nature. Because it normally has a positively charged nitrogen at its end, lysine can bind the negatively charged phosphates of the DNA backbone. The acetylation event converts the positively charged amine group on the side chain into a neutral amide linkage. This removes the positive charge, thus loosening the DNA from the histone. When this occurs, complexes like [SWI/SNF](#) and other transcriptional factors can bind to the DNA and allow transcription to occur. This is the "cis" model of the epigenetic function. In other words, changes to the histone tails have a direct effect on the DNA itself.^[36]

Another model of epigenetic function is the "trans" model. In this model, changes to the histone tails act indirectly on the DNA. For example, lysine acetylation may create a binding site for chromatin-modifying enzymes (or transcription machinery as well). This chromatin remodeler can then cause changes to the state of the chromatin. Indeed, a bromodomain – a protein domain that specifically binds acetyl-lysine – is found in many enzymes that help activate transcription, including the [SWI/SNF](#) complex. It may be that acetylation acts in this and the previous way to aid in transcriptional activation.

The idea that modifications act as docking modules for related factors is borne out by [histone methylation](#) as well. Methylation of lysine 9 of histone H3 has long been associated with constitutively transcriptionally silent chromatin (constitutive [heterochromatin](#)) (see bottom Figure). It has been determined that a chromodomain (a domain that specifically binds methyl-lysine) in the transcriptionally repressive protein [HP1](#) recruits HP1 to K9 methylated regions. One example that seems to refute this biophysical model for methylation is that tri-methylation of histone H3 at lysine 4 is strongly associated with (and required for full) transcriptional activation (see top Figure). Tri-methylation, in this case, would introduce a fixed positive charge on the tail.

It has been shown that the histone lysine methyltransferase (KMT) is responsible for this methylation activity in the pattern of histones H3 & H4. This enzyme utilizes a catalytically active site called the SET domain (Suppressor of variegation, Enhancer of Zeste, Trithorax). The SET domain is a 130-amino acid sequence involved in modulating gene activities. This domain has been demonstrated to bind to the histone tail and causes the methylation of the histone.

Differing histone modifications are likely to function in differing ways; acetylation at one position is likely to function differently from acetylation at another position. Also, multiple modifications may occur at the same time, and these modifications may work together to change the behavior of the [nucleosome](#). The idea that multiple dynamic modifications regulate gene transcription in a systematic and reproducible way is called the [histone code](#), although the idea that histone state can be read linearly as a digital information carrier has been largely debunked. One of the best-understood systems that orchestrate chromatin-based silencing is the [SIR protein](#) based silencing of the yeast hidden mating-type loci HML and HMR.

DNA methylation

[\[edit\]](#)

Further information: [Methylation](#)

[DNA methylation](#) frequently occurs in repeated sequences, and helps to suppress the expression and mobility of '[transposable elements](#)':^[38] Because [5-methylcytosine](#) can be spontaneously deaminated (replacing nitrogen by oxygen) to [thymidine](#), CpG sites are frequently mutated and become rare in the genome, except at [CpG islands](#) where they remain unmethylated. Epigenetic changes of this type thus have the potential to direct increased frequencies of permanent genetic mutation. DNA methylation patterns are known to be established and modified in response to environmental factors by a complex interplay of at least three independent [DNA methyltransferases](#), DNMT1, DNMT3A, and DNMT3B, the loss of any of which is lethal in mice.^[39] DNMT1 is the most abundant methyltransferase in somatic cells,^[40] localizes to replication foci,^[41] has a 10–40-fold preference for hemimethylated DNA and interacts with the [proliferating cell nuclear antigen](#) (PCNA).^[42]

By preferentially modifying hemimethylated DNA, DNMT1 transfers patterns of methylation to a newly synthesized strand after [DNA replication](#), and therefore is often referred to as the 'maintenance' methyltransferase.^[43] DNMT1 is essential for proper embryonic development, imprinting and X-inactivation.^{[39][44]} To emphasize the difference of this molecular mechanism of inheritance from the canonical Watson-Crick base-pairing mechanism of transmission of genetic information, the term 'Epigenetic templating' was introduced.^[45] Furthermore, in addition to the maintenance and transmission of methylated DNA states, the same principle could work in the maintenance and transmission of histone modifications and even cytoplasmic ([structural](#)) heritable states.^[46]

RNA methylation

[\[edit\]](#)

Further information: [Methylation](#)

RNA methylation of N6-methyladenosine (m6A) as the most abundant eukaryotic RNA modification has recently been recognized as an important gene regulatory mechanism.^[47]

Histone modifications

[\[edit\]](#)

Histones H3 and H4 can also be manipulated through demethylation using [histone lysine demethylase](#)(KDM). This recently identified enzyme has a catalytically active site called the Jumonji domain (JmjC). The demethylation occurs when JmjC utilizes multiple cofactors to hydroxylate the methyl group, thereby removing it. JmjC is capable of demethylating mono-, di-, and tri-methylated substrates.^[48]

Chromosomal regions can adopt stable and heritable alternative states resulting in bistable gene expression without changes to the DNA sequence. Epigenetic control is often associated with alternative [covalent modifications](#) of histones.^[49] The stability and heritability of states of larger chromosomal regions are suggested to involve positive feedback where modified [nucleosomes](#) recruit enzymes that similarly modify nearby nucleosomes.^[50] A simplified stochastic model for this type of epigenetics is found here.^{[51][52]}

It has been suggested that chromatin-based transcriptional regulation could be mediated by the effect of small RNAs. [Small interfering RNAs](#) can modulate transcriptional gene expression via epigenetic modulation of targeted [promoters](#).^[53]

RNA transcripts

[\[edit\]](#)

Sometimes, a gene, once activated, transcribes a product that directly or indirectly sustains its own activity. For example, [Hnf4](#) and [MyoD](#) enhance the transcription of many liver-specific and muscle-specific genes, respectively, including their own, through the [transcription factor](#) activity of the [proteins](#) they encode. RNA signalling includes differential recruitment of a hierarchy of generic chromatin modifying complexes and DNA methyltransferases to specific loci by RNAs during differentiation and development.^[54] Other epigenetic changes are mediated by the production of [different splice forms](#) of [RNA](#), or by formation of double-stranded RNA ([RNAi](#)). Descendants of the cell in which the gene was turned on will inherit this activity, even if the original stimulus for gene-activation is no longer present. These genes are often turned on or off by [signal transduction](#), although in some systems where [syncytia](#) or [gap junctions](#) are important, RNA may spread directly to other cells or nuclei by [diffusion](#). A large amount of RNA and protein is contributed to the [zygote](#) by the mother during [oogenesis](#) or via [nurse cells](#), resulting in [maternal effect](#) phenotypes. A smaller quantity of sperm RNA is transmitted from the father, but there is recent evidence that this epigenetic information can lead to visible changes in several generations of offspring.^[55]

MicroRNAs

[\[edit\]](#)

[MicroRNAs](#) (miRNAs) are members of [non-coding RNAs](#) that range in size from 17 to 25 nucleotides. miRNAs regulate a large variety of biological functions in plants and animals.^[56] So far, in 2013, about 2000 miRNAs have been discovered in humans and these can be found online in a miRNA database.^[57] Each miRNA expressed in a cell may target about 100 to 200 messenger RNAs(mRNAs) that it downregulates.^[58] Most of the downregulation of mRNAs occurs by causing the decay of the targeted mRNA, while some downregulation occurs at the level of translation into protein.^[59]

It appears that about 60% of human protein coding genes are regulated by miRNAs.^[60] Many miRNAs are epigenetically regulated. About 50% of miRNA genes are associated with [CpG islands](#),^[56] that may be repressed by epigenetic methylation. Transcription from methylated CpG islands is strongly and heritably repressed.^[61] Other miRNAs are epigenetically regulated by either histone modifications or by combined DNA methylation and histone modification.^[56]

mRNA

[\[edit\]](#)

In 2011, it was demonstrated that the [methylation](#) of [mRNA](#) plays a critical role in human [energy homeostasis](#). The obesity-associated [FTO gene](#) is shown to be able to [demethylate N6-methyladenosine](#) in RNA.^{[62][63]}

sRNAs

[\[edit\]](#)

[sRNAs](#) are small (50–250 nucleotides), highly structured, non-coding RNA fragments found in bacteria. They control gene expression including [virulence](#) genes in pathogens and are viewed as new targets in the fight against drug-resistant bacteria.^[64] They play an important role in many biological processes, binding to mRNA and protein targets in prokaryotes. Their phylogenetic analyses, for example through sRNA–mRNA target interactions or protein [binding properties](#), are used to build comprehensive databases.^[65] sRNA-[gene maps](#) based on their targets in microbial genomes are also constructed.^[66]

Long non-coding RNAs

[\[edit\]](#)

Numerous investigations have demonstrated the pivotal involvement of long non-coding RNAs (lncRNAs) in the regulation of gene expression and chromosomal modifications, thereby exerting significant control over cellular differentiation. These long non-coding RNAs also contribute to genomic imprinting and the inactivation of the X chromosome.^[67] In invertebrates such as social insects of honey bees, long non-coding RNAs are detected as a possible epigenetic mechanism via allele-specific genes underlying aggression via reciprocal crosses.^[68]

Prions

[\[edit\]](#)

Further information: [Fungal prions](#)

[Prions](#) are [infectious](#) forms of [proteins](#). In general, proteins fold into discrete units that perform distinct cellular functions, but some proteins are also capable of forming an infectious conformational state known as a prion. Although often viewed in the context of [infectious disease](#), prions are more loosely defined by their ability to catalytically convert other native state versions of the same protein to an infectious conformational state. It is in this latter sense that they can be viewed as epigenetic agents capable of inducing a phenotypic change without a modification of the genome.^[69]

[Fungal prions](#) are considered by some to be epigenetic because the infectious phenotype caused by the prion can be inherited without modification of the genome. [PSI+](#) and URE3, discovered in [yeast](#) in 1965 and 1971, are the two best studied of this type of prion.^{[70][71]} Prions can have a phenotypic effect through the sequestration of protein in aggregates, thereby reducing that protein's activity. In PSI+ cells, the loss of the Sup35 protein (which is involved in termination of translation) causes ribosomes to have a higher rate of read-through of stop [codons](#), an effect that results in suppression of [nonsense mutations](#) in other genes.^[72] The ability of Sup35 to form prions may be a conserved trait. It could confer an adaptive advantage by giving cells the ability to [switch into a PSI+ state](#) and express dormant genetic features normally terminated by stop codon mutations.^{[73][74][75][76]}

Prion-based epigenetics has also been observed in [Saccharomyces cerevisiae](#).^[77]

Molecular basis

[\[edit\]](#)

Epigenetic changes modify the activation of certain genes, but not the genetic code sequence of DNA.^[78] The microstructure (not code) of DNA itself or the associated [chromatin](#) proteins may be modified, causing activation or silencing. This mechanism enables differentiated cells in a multicellular organism to express only the genes that are necessary for their own activity. Epigenetic changes are preserved when cells divide. Most epigenetic changes only occur within the course of one individual organism's lifetime; however, these epigenetic changes can be transmitted to the organism's offspring through a process called [transgenerational epigenetic inheritance](#). Moreover, if gene inactivation occurs in a sperm or egg cell that results in fertilization, this epigenetic modification may also be transferred to the next generation.^[79]

Specific epigenetic processes include [paramutation](#), [bookmarking](#), [imprinting](#), [gene silencing](#), [X chromosome inactivation](#), [position effect](#), [DNA methylation reprogramming](#), [transvection](#), [maternal effects](#), the progress of [carcinogenesis](#), many effects of [teratogens](#), regulation of [histone](#) modifications and [heterochromatin](#), and technical limitations affecting [parthenogenesis](#) and [cloning](#).^{[80][81][82]}

DNA damage

[\[edit\]](#)

DNA damage can also cause epigenetic changes.^{[83][84][85]} DNA damage is very frequent, occurring on average about 60,000 times a day per cell of the human body (see [DNA damage \(naturally occurring\)](#)). These damages are largely repaired, however, epigenetic changes can still remain at the site of DNA repair.^[86] In particular, a double strand break in DNA can initiate unprogrammed epigenetic gene silencing both by causing DNA methylation as well as by promoting silencing types of histone modifications (chromatin remodeling - see next section).^[87] In addition, the enzyme [Parp1 \(poly\(ADP-ribose polymerase\)](#) and its product poly(ADP-ribose (PAR) accumulate at sites of DNA damage as part of the repair process.^[88] This accumulation, in turn, directs recruitment and activation of the chromatin remodeling protein, ALC1, that can cause [nucleosome](#) remodeling.^[89] Nucleosome remodeling has been found to cause, for instance, epigenetic silencing of DNA repair gene MLH1.^{[22][90]} DNA damaging chemicals, such as [benzene](#), [hydroquinone](#), [styrene](#), [carbon tetrachloride](#) and [trichloroethylene](#), cause considerable hypomethylation of DNA, some through the activation of oxidative stress pathways.^[91]

Foods are known to alter the epigenetics of rats on different diets.^[92] Some food components epigenetically increase the levels of DNA repair enzymes such as [MGMT](#) and [MLH1](#)^[93] and [p53](#).^[94] Other food components can reduce DNA damage, such as soy [isoflavones](#). In one study, markers for oxidative stress, such as modified nucleotides that can result from DNA damage, were decreased by a 3-week diet supplemented with soy.^[95] A decrease in oxidative DNA damage was also observed 2 h after consumption of [anthocyanin](#)-rich [bilberry \(Vaccinium myrtillus L.\) pomace](#) extract.^[96]

DNA repair

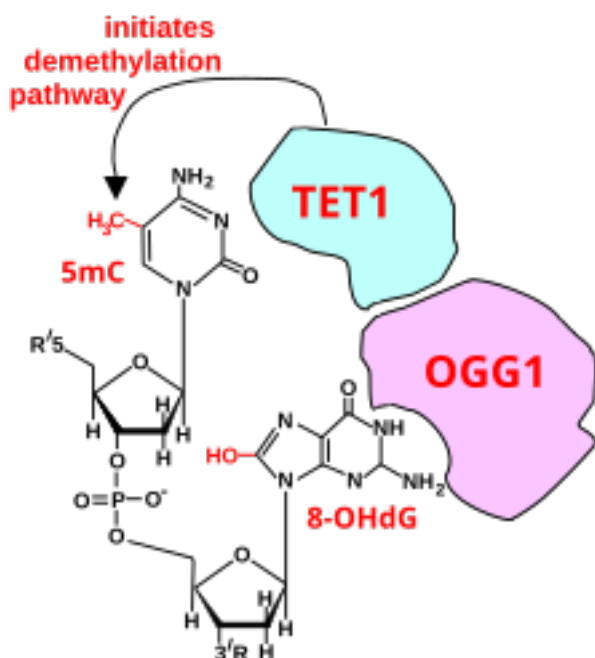
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Damage to DNA is very common and is constantly being repaired. Epigenetic alterations can accompany DNA repair of oxidative damage or double-strand breaks. In human cells, oxidative DNA damage occurs about 10,000 times a day and DNA double-strand breaks occur about 10 to 50 times a cell cycle in somatic replicating cells (see [DNA damage \(naturally occurring\)](#)). The selective advantage of DNA repair is to allow the cell to survive in the face of DNA damage. The selective advantage of epigenetic alterations that occur with DNA repair is not clear.^[citation needed]

Repair of oxidative DNA damage can alter epigenetic markers

[edit]

In the steady state (with endogenous damages occurring and being repaired), there are about 2,400 oxidatively damaged guanines that form [8-oxo-2'-deoxyguanosine](#) (8-OHdG) in the average mammalian cell DNA.^[97] 8-OHdG constitutes about 5% of the oxidative damages commonly present in DNA.^[98] The oxidized guanines do not occur randomly among all guanines in DNA. There is a sequence preference for the guanine at a [methylated CpG site](#) (a cytosine followed by guanine along its [5' → 3' direction](#) and where the cytosine is methylated (5-mCpG)).^[99] A 5-mCpG site has the lowest ionization potential for guanine oxidation.^[citation needed]



Initiation of [DNA demethylation](#) at a [CpG site](#). In adult somatic cells DNA methylation typically occurs in the context of CpG dinucleotides ([CpG sites](#)), forming [5-methylcytosine](#)-pG, or 5mCpG. Reactive oxygen species (ROS) may attack guanine at the dinucleotide site, forming [8-hydroxy-2'-deoxyguanosine](#) (8-OHdG), and resulting in a 5mCp-8-OHdG dinucleotide site. The [base excision repair](#) enzyme [OGG1](#) targets 8-OHdG and binds to the lesion without immediate excision. OGG1, present at a 5mCp-8-OHdG site recruits [TET1](#) and TET1 oxidizes the 5mC adjacent to the 8-OHdG. This initiates demethylation of 5mC.^[100]

Oxidized guanine has mispairing potential and is mutagenic.^[101] [Oxoguanine glycosylase](#) (OGG1) is the primary enzyme responsible for the excision of the oxidized guanine during DNA repair. OGG1 finds and binds to an 8-OHdG within a few seconds.^[102] However, OGG1 does not immediately excise 8-OHdG. In HeLa cells half maximum removal of 8-OHdG occurs in 30 minutes,^[103] and in irradiated mice, the 8-OHdGs induced in the mouse liver are removed with a half-life of 11 minutes.^[98]

When OGG1 is present at an oxidized guanine within a methylated [CpG site](#) it recruits [TET1](#) to the 8-OHdG lesion (see Figure). This allows TET1 to demethylate an adjacent methylated cytosine. Demethylation of cytosine is an epigenetic alteration.^[citation needed]

As an example, when human mammary epithelial cells were treated with H₂O₂ for six hours, 8-OHdG increased about 3.5-fold in DNA and this caused about 80% demethylation of the 5-methylcytosines in the genome.^[100] Demethylation of CpGs in a gene promoter by [TET enzyme](#) activity increases transcription of the gene into messenger RNA.^[104] In cells treated with H₂O₂, one particular gene was examined, [BACE1](#).^[100] The methylation level of the [BACE1 CpG island](#) was reduced (an epigenetic alteration) and this allowed about 6.5 fold increase of expression of [BACE1](#) messenger RNA.^[citation needed]

While six-hour incubation with H₂O₂ causes considerable demethylation of 5-mCpG sites, shorter times of H₂O₂ incubation appear to promote other epigenetic alterations. Treatment of cells with H₂O₂ for 30 minutes causes the mismatch repair protein heterodimer MSH2-MSH6 to recruit DNA methyltransferase 1 ([DNMT1](#)) to sites of some kinds of oxidative DNA damage.^[105] This could cause increased methylation of cytosines (epigenetic alterations) at these locations.

Jiang et al.^[106] treated [HEK 293 cells](#) with agents causing oxidative DNA damage, ([potassium bromate](#)(KBrO₃) or [potassium chromate](#) (K₂CrO₄)). [Base excision repair](#) (BER) of oxidative damage occurred with the DNA repair enzyme [polymerase beta](#) localizing to oxidized guanines. Polymerase beta is the main human polymerase in short-patch BER of oxidative DNA damage. Jiang et al.^[106] also found that polymerase beta recruited the [DNA methyltransferase](#) protein DNMT3b to BER repair sites. They then evaluated the methylation pattern at the single nucleotide level in a small region of DNA including the [promoter](#) region and the early transcription region of the [BRCA1](#) gene. Oxidative DNA damage from bromate modulated the DNA methylation pattern (caused epigenetic alterations) at CpG sites within the region of DNA studied. In untreated cells, CpGs located at -189, -134, -29, -19, +16, and +19 of the BRCA1 gene had methylated cytosines (where numbering is from the [messenger RNA](#) transcription start site, and negative numbers indicate nucleotides in the upstream [promoter](#) region). Bromate treatment-induced oxidation resulted in the loss of cytosine methylation at -189, -134, +16 and +19 while also leading to the formation of new methylation at the CpGs located at -80, -55, -21 and +8 after DNA repair was allowed.

Homologous recombinational repair alters epigenetic markers

[\[edit\]](#)

At least four articles report the recruitment of [DNA methyltransferase 1 \(DNMT1\)](#) to sites of DNA double-strand breaks.^{[107][108][109][110]} During [homologous recombinational repair \(HR\)](#) of the double-strand break, the involvement of DNMT1 causes the two repaired strands of DNA to have different levels of methylated cytosines. One strand becomes frequently methylated at about 21 [CpG sites](#) downstream of the repaired double-strand break. The other DNA strand loses methylation at about six CpG sites that were previously methylated downstream of the double-strand break, as well as losing methylation at about five CpG sites that were previously methylated upstream of the double-strand break. When the chromosome is replicated, this gives rise to one daughter chromosome that is heavily methylated downstream of the previous break site and one that is unmethylated in the region both upstream and downstream of the previous break site. With respect to the gene that was broken by the double-strand break, half of the progeny cells express that gene at a high level and in the other half of the progeny cells expression of that gene is repressed. When clones of these cells were maintained for three years, the new methylation patterns were maintained over that time period.^[111]

In mice with a CRISPR-mediated homology-directed recombination insertion in their genome there were a large number of increased methylations of CpG sites within the double-strand break-associated insertion.^[112]

Non-homologous end joining can cause some epigenetic marker alterations

[\[edit\]](#)

[Non-homologous end joining](#) (NHEJ) repair of a double-strand break can cause a small number of demethylations of pre-existing cytosine DNA methylations downstream of the repaired double-strand break.^[108] Further work by Allen et al.^[113] showed that NHEJ of a DNA double-strand break in a cell could give rise to some progeny cells having repressed expression of the gene harboring the initial double-strand break and some progeny having high expression of that gene due to epigenetic alterations associated with NHEJ repair. The frequency of epigenetic alterations causing repression of a gene after an NHEJ repair of a DNA double-strand break in that gene may be about 0.9%.^[109]

Techniques used to study epigenetics

[\[edit\]](#)

Epigenetic research uses a wide range of [molecular biological](#) techniques to further understanding of epigenetic phenomena. These techniques include [chromatin immunoprecipitation](#) (together with its large-scale variants [ChIP-on-chip](#) and [ChIP-Seq](#)), [fluorescent in situ hybridization](#), methylation-sensitive [restriction enzymes](#), DNA adenine methyltransferase identification ([DamID](#)) and [bisulfite sequencing](#).^[114] Furthermore, the use of [bioinformatics](#) methods has a role in [computational epigenetics](#).^[114]

Chromatin Immunoprecipitation

[\[edit\]](#)

Chromatin Immunoprecipitation (ChIP) has helped bridge the gap between DNA and epigenetic interactions.^[115] With the use of ChIP, researchers are able to make findings in regards to gene regulation, transcription mechanisms, and chromatin structure.^[115]

Fluorescent *in situ* hybridization

[\[edit\]](#)

Fluorescent *in situ* hybridization (FISH) is very important to understand epigenetic mechanisms.^[116] FISH can be used to find the location of genes on chromosomes, as well as finding noncoding RNAs.^{[116][117]} FISH is predominantly used for detecting chromosomal abnormalities in humans.^[117]

Methylation-sensitive restriction enzymes

[\[edit\]](#)

Methylation sensitive restriction enzymes paired with PCR is a way to evaluate methylation in DNA - specifically the CpG sites.^[118] If DNA is methylated, the restriction enzymes will not cleave the strand.^[118] Contrarily, if the DNA is not methylated, the enzymes will cleave the strand and it will be amplified by PCR.^[118]

Bisulfite sequencing

[\[edit\]](#)

Bisulfite sequencing is another way to evaluate DNA methylation. Cytosine will be changed to uracil from being treated with sodium bisulfite, whereas methylated cytosines will not be affected.^{[118][119][120]}

Nanopore sequencing

[\[edit\]](#)

Certain sequencing methods, such as [nanopore sequencing](#), allow sequencing of native DNA. Native (=unamplified) DNA retains the epigenetic modifications which would otherwise be lost during the amplification step. Nanopore basecaller models can distinguish between the signals obtained for epigenetically modified bases and unaltered based and provide an epigenetic profile in addition to the sequencing result.^[121]

Structural inheritance

[\[edit\]](#)

Further information: [Structural inheritance](#)

In [ciliates](#) such as [Tetrahymena](#) and [Paramecium](#), genetically identical cells show heritable differences in the patterns of ciliary rows on their cell surface. Experimentally altered patterns can be transmitted to daughter cells. It seems existing structures act as

templates for new structures. The mechanisms of such inheritance are unclear, but reasons exist to assume that multicellular organisms also use existing cell structures to assemble new ones.^{[122][123][124]}

Nucleosome positioning

[\[edit\]](#)

Eukaryotic genomes have numerous [nucleosomes](#). Nucleosome position is not random, and determine the accessibility of DNA to regulatory proteins. Promoters active in different tissues have been shown to have different nucleosome positioning features.^[125] This determines differences in gene expression and cell differentiation. It has been shown that at least some nucleosomes are retained in sperm cells (where most but not all histones are replaced by [protamines](#)). Thus nucleosome positioning is to some degree inheritable. Recent studies have uncovered connections between nucleosome positioning and other epigenetic factors, such as DNA methylation and hydroxymethylation.^[126]

Histone variants

[\[edit\]](#)

Different [histone variants](#) are incorporated into specific regions of the genome non-randomly. Their differential biochemical characteristics can affect genome functions via their roles in gene regulation,^[127] and maintenance of chromosome structures.^[128]

Genomic architecture

[\[edit\]](#)

The three-dimensional configuration of the genome (the 3D genome) is complex, dynamic and crucial for regulating genomic function and nuclear processes such as DNA replication, transcription and DNA-damage repair.^[129]

Functions and consequences

[\[edit\]](#)

In the brain

[\[edit\]](#)

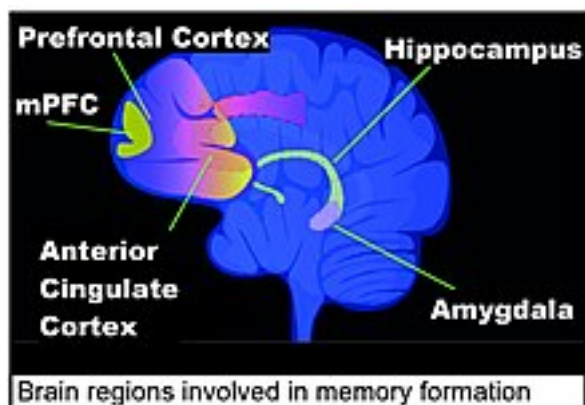
Memory

[\[edit\]](#)

Main article: [Epigenetics in learning and memory](#)

[Memory formation](#) and maintenance are due to epigenetic alterations that cause the required dynamic changes in [gene transcription](#) that create and renew memory in neurons.^[31]

An event can set off a chain of reactions that result in altered methylations of a large set of genes in neurons, which give a representation of the event, a memory.^[31]

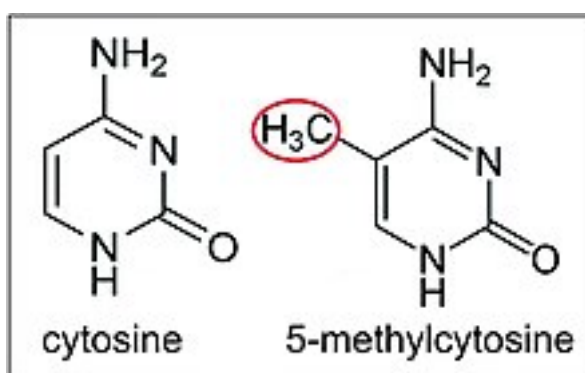


including medial prefrontal cortex (mPFC)

Areas of the brain important in the formation of memories include the hippocampus, medial prefrontal cortex (mPFC), anterior cingulate cortex and amygdala, as shown in the diagram of the human brain in this section.^[130]

When a strong memory is created, as in a rat subjected to [contextual fear conditioning](#) (CFC), one of the earliest events to occur is that more than 100 DNA double-strand breaks are formed by [topoisomerase IIB](#) in neurons of the hippocampus and the medial prefrontal cortex (mPFC).^[131] These double-strand breaks are at specific locations that allow activation of transcription of [immediate early genes](#) (IEGs) that are important in memory formation, allowing their expression in [mRNA](#), with peak mRNA transcription at seven to ten minutes after CFC.^{[131][132]}

Two important IEGs in memory formation are [EGR1](#)^[133] and [the alternative promoter variant of DNMT3A, DNMT3A2](#).^[134] EGR1 protein binds to DNA at its binding motifs, 5'-GCGTGGGCG-3' or 5'-GCGGGGGCGG-3', and there are about 12,000 genome locations at which EGR1 protein can bind.^[135] EGR1 protein binds to DNA in gene [promoter](#) and [enhancer](#) regions. EGR1 recruits the demethylating enzyme [TET1](#) to an association, and brings TET1 to about 600 locations on the genome where TET1 can then demethylate and activate the associated genes.^[135]



Cytosine and 5-methylcytosine

The DNA methyltransferases DNMT3A1, DNMT3A2 and DNMT3B can all methylate cytosines (see image this section) at [CpG sites](#) in or near the promoters of genes. As shown by Manzo et al.,^[136] these three DNA methyltransferases differ in their genomic binding locations and DNA methylation activity at different regulatory sites. Manzo et al. located 3,970 genome regions exclusively enriched for DNMT3A1, 3,838 regions for DNMT3A2 and 3,432 regions for DNMT3B. When DNMT3A2 is newly induced as an IEG (when neurons are activated), many new cytosine methylations occur, presumably in the target regions of DNMT3A2. Oliviera et al.^[134] found that the neuronal activity-inducible IEG levels of Dnmt3a2 in the hippocampus determined the ability to form long-term memories.

Rats form long-term associative memories after [contextual fear conditioning \(CFC\)](#).^[137] Duke et al.^[30] found that 24 hours after CFC in rats, in hippocampus neurons, 2,097 genes (9.17% of the genes in the rat genome) had altered methylation. When newly

methylated cytosines are present in [CpG sites](#) in the promoter regions of genes, the genes are often repressed, and when newly demethylated cytosines are present the genes may be activated.^[138] After CFC, there were 1,048 genes with reduced mRNA expression and 564 genes with upregulated mRNA expression. Similarly, when mice undergo CFC, one hour later in the hippocampus region of the mouse brain there are 675 demethylated genes and 613 hypermethylated genes.^[139] However, memories do not remain in the hippocampus, but after four or five weeks the memories are stored in the anterior cingulate cortex.^[140] In the studies on mice after CFC, Halder et al.^[139] showed that four weeks after CFC there were at least 1,000 differentially methylated genes and more than 1,000 differentially expressed genes in the anterior cingulate cortex, while at the same time the altered methylations in the hippocampus were reversed.

The epigenetic alteration of methylation after a new memory is established creates a different pool of nuclear mRNAs. As reviewed by Bernstein,^[31] the epigenetically determined new mix of nuclear [mRNAs](#) are often packaged into neuronal granules, or [messenger RNP](#), consisting of mRNA, [small and large ribosomal subunits](#), translation initiation factors and RNA-binding proteins that regulate mRNA function. These neuronal granules are transported from the neuron nucleus and are directed, according to 3' untranslated regions of the mRNA in the granules (their "zip codes"), to neuronal [dendrites](#). Roughly 2,500 mRNAs may be localized to the dendrites of hippocampal pyramidal neurons and perhaps 450 transcripts are in excitatory presynaptic nerve terminals (dendritic spines). The altered assortments of transcripts (dependent on epigenetic alterations in the neuron nucleus) have different sensitivities in response to signals, which is the basis of altered synaptic plasticity. Altered synaptic plasticity is often considered the neurochemical foundation of learning and memory.

Aging

[\[edit\]](#)

See also: [DNA methylation § In aging](#), and [Hallmarks of aging § Epigenomic alterations](#)

Epigenetics play a major role in [brain aging](#) and age-related cognitive decline, with relevance to [life extension](#).^{[141][142][143][144][145]}

Other and general

[\[edit\]](#)

In adulthood, changes in the [epigenome](#) are important for various higher cognitive functions. Dysregulation of epigenetic mechanisms is implicated in [neurodegenerative disorders](#) and diseases. Epigenetic modifications in [neurons](#) are dynamic and reversible.^[146] Epigenetic regulation impacts neuronal action, affecting learning, memory, and other [cognitive](#) processes.^[147]

Early events, including during [embryonic development](#), can influence development, cognition, and health outcomes through [epigenetic mechanisms](#).^[148]

Epigenetic mechanisms have been proposed as "a potential molecular mechanism for effects of endogenous [hormones](#) on the organization of developing brain circuits".^[149]

[Nutrients](#) could interact with the epigenome to "protect or boost cognitive processes across the lifespan".^{[150][151]}

A review suggests [neurobiological effects of physical exercise](#) via [epigenetics](#) seem "central to building an 'epigenetic memory' to influence long-term brain function and behavior" and may even be heritable.^[152]

With the axo-ciliary [synapse](#), there is communication between [serotonergic axons](#) and antenna-like [primary cilia](#) of [CA1 pyramidal neurons](#) that alters the neuron's [epigenetic](#) state in the [nucleus](#) via the signalling distinct from that at the [plasma membrane](#) (and longer-term).^{[153][154]}

Epigenetics also play a major role in the [brain evolution in and to humans](#).^[155]

Development

[\[edit\]](#)

Developmental epigenetics can be divided into predetermined and probabilistic epigenesis. Predetermined epigenesis is a unidirectional movement from structural development in DNA to the functional maturation of the protein. "Predetermined" here means that development is scripted and predictable. Probabilistic epigenesis on the other hand is a bidirectional structure-function development with experiences and external molding development.^[156]

Somatic epigenetic inheritance, particularly through DNA and histone covalent modifications and [nucleosome](#) repositioning, is very important in the development of multicellular eukaryotic organisms.^[126] The genome sequence is static (with some notable exceptions), but cells differentiate into many different types, which perform different functions, and respond differently to the environment and intercellular signaling. Thus, as individuals develop, [morphogens](#) activate or silence genes in an epigenetically heritable fashion, giving cells a memory. In mammals, most cells terminally differentiate, with only [stem cells](#) retaining the ability to differentiate into several cell types ("totipotency" and "multipotency"). In [mammals](#), some stem cells continue producing newly differentiated cells throughout life, such as in [neurogenesis](#), but mammals are not able to respond to loss of some tissues, for example, the inability to regenerate limbs, which some other animals are capable of. Epigenetic modifications regulate the transition from neural stem cells to glial progenitor cells (for example, differentiation into oligodendrocytes is regulated by the deacetylation and methylation of histones).^[157] Unlike animals, plant cells do not terminally differentiate, remaining totipotent with the ability to give rise to a new individual plant. While plants do utilize many of the same epigenetic mechanisms as animals, such as [chromatin remodeling](#), it has been hypothesized that some kinds of plant cells do not use or require "cellular memories", resetting their gene expression patterns using positional information from the environment and surrounding cells to determine their fate.^[158]

Epigenetic changes can occur in response to environmental exposure – for example, maternal dietary supplementation with [genistein](#) (250 mg/kg) have epigenetic changes affecting expression of the [agouti gene](#), which affects their fur color, weight, and propensity to develop cancer.^{[159][160][161]} Ongoing research is focused on exploring the impact of other known [teratogens](#), such as [diabetic embryopathy](#), on [methylation](#) signatures.^[162]

Controversial results from one study suggested that traumatic experiences might produce an epigenetic signal that is capable of being passed to future generations. Mice were trained, using foot shocks, to fear a cherry blossom odor. The investigators reported that the mouse offspring had an increased aversion to this specific odor.^{[163][164]} They suggested epigenetic changes that increase gene expression, rather than in DNA itself, in a gene, M71, that governs the functioning of an odor receptor in the nose that responds specifically to this cherry blossom smell. There were physical changes that correlated with olfactory (smell) function in the brains of the trained mice and their descendants. Several criticisms were reported, including the study's low statistical power as evidence of some irregularity such as bias in reporting results.^[165] Due to limits of sample size, there is a probability that an effect will not be demonstrated to within statistical significance even if it exists. The criticism suggested that the probability that all the experiments reported would show positive results if an identical protocol was followed, assuming the claimed effects exist, is merely 0.4%. The authors also did not indicate which mice were siblings, and treated all of the mice as statistically independent.^[166] The original researchers pointed out negative results in the paper's appendix that the criticism omitted in its calculations, and undertook to track which mice were siblings in the future.^[167]

Transgenerational

[\[edit\]](#)

Main article: [Transgenerational epigenetic inheritance](#)

Epigenetic mechanisms were a necessary part of the evolutionary origin of [cell differentiation](#).^[168]^[need quotation to verify] Although epigenetics in multicellular organisms is generally thought to be a mechanism involved in differentiation, with epigenetic patterns "reset" when organisms reproduce, there have been some observations of transgenerational epigenetic inheritance (e.g., the phenomenon of [paramutation](#) observed in [maize](#)). Although most of these multigenerational epigenetic traits are gradually lost over several generations, the possibility remains that multigenerational epigenetics could be another aspect to [evolution](#) and adaptation. As mentioned above, some define epigenetics as heritable.

A sequestered germ line or [Weismann barrier](#) is specific to animals, and epigenetic inheritance is more common in plants and microbes. [Eva Jablonka](#), [Marion J. Lamb](#) and Étienne Danchin have argued that these effects may require enhancements to the standard conceptual framework of the [modern synthesis](#) and have called for an [extended evolutionary synthesis](#).^[169]^[170]^[171] Other evolutionary biologists, such as [John Maynard Smith](#), have incorporated epigenetic inheritance into [population-genetics](#) models^[172] or are openly skeptical of the extended evolutionary synthesis ([Michael Lynch](#)).^[173] Thomas Dickins and Qazi Rahman state that epigenetic mechanisms such as DNA methylation and histone modification are genetically inherited under the control of [natural selection](#) and therefore fit under the earlier "[modern synthesis](#)".^[174]

Two important ways in which epigenetic inheritance can differ from traditional genetic inheritance, with important consequences for evolution, are:

- rates of epimutation can be much faster than rates of mutation^[175]
- the epimutations are more easily reversible^[176]

In plants, heritable DNA methylation mutations are 100,000 times more likely to occur compared to DNA mutations.^[177] An epigenetically inherited element such as the [PSI+](#) system can act as a "stop-gap", good enough for short-term adaptation that allows the lineage to survive for long enough for mutation and/or recombination to [genetically assimilate](#) the adaptive phenotypic change.^[178] The existence of this possibility increases the [evolvability](#) of a species.

More than 100 cases of [transgenerational epigenetic inheritance](#) phenomena have been reported in a wide range of organisms, including prokaryotes, plants, and animals.^[179] For instance, [mourning-cloak butterflies](#) will change color through hormone changes in response to experimentation of varying temperatures.^[180]

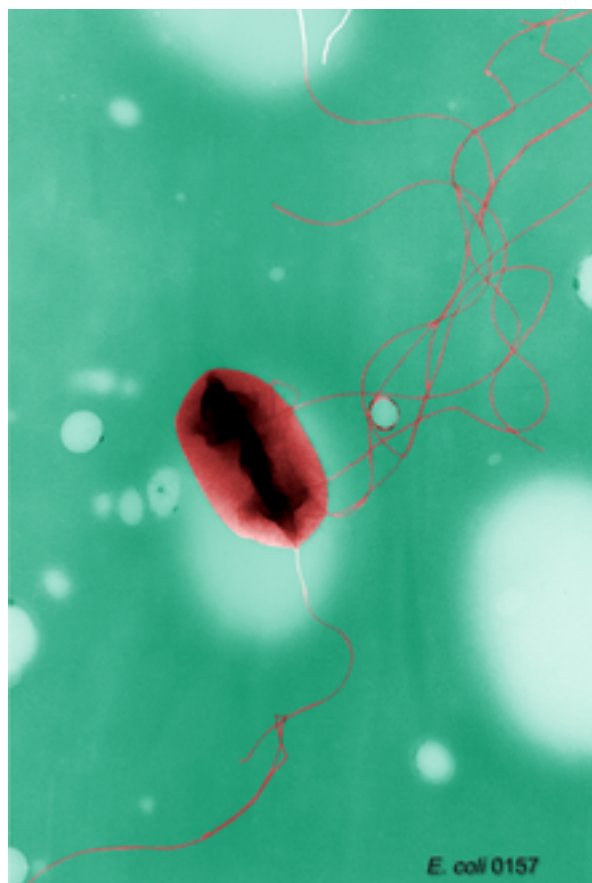
The filamentous fungus *Neurospora crassa* is a prominent model system for understanding the control and function of cytosine methylation. In this organism, DNA methylation is associated with relics of a genome-defense system called RIP (repeat-induced point mutation) and silences gene expression by inhibiting transcription elongation.^[181]

The [yeast prion](#) PSI is generated by a conformational change of a translation termination factor, which is then inherited by daughter cells. This can provide a survival advantage under adverse conditions, exemplifying epigenetic regulation which enables unicellular organisms to respond rapidly to environmental stress. Prions can be viewed as epigenetic agents capable of inducing a phenotypic change without modification of the genome.^[182]

Direct detection of epigenetic marks in microorganisms is possible with [single molecule real time sequencing](#), in which polymerase sensitivity allows for measuring methylation and other modifications as a DNA molecule is being sequenced.^[183] Several projects have demonstrated the ability to collect genome-wide epigenetic data in bacteria.^[184]^[185]^[186]^[187]

Epigenetics in bacteria

[\[edit\]](#)



Escherichia coli bacteria

While epigenetics is of fundamental importance in [eukaryotes](#), especially [metazoans](#), it plays a different role in bacteria.^[188] Most importantly, eukaryotes use epigenetic mechanisms primarily to regulate gene expression which bacteria rarely do. However, bacteria make widespread use of postreplicative DNA methylation for the epigenetic control of DNA-protein interactions. Bacteria also use DNA [adenine](#) methylation (rather than DNA [cytosine](#) methylation) as an epigenetic signal. DNA adenine methylation is important in bacteria virulence in organisms such as [Escherichia coli](#), [Salmonella](#), [Vibrio](#), [Yersinia](#), [Haemophilus](#), and [Brucella](#). In [Alphaproteobacteria](#), methylation of adenine regulates the cell cycle and couples gene transcription to DNA replication. In [Gammaproteobacteria](#), adenine methylation provides signals for DNA replication, chromosome segregation, mismatch repair, packaging of bacteriophage, transposase activity and regulation of gene expression.^{[182][189]} There exists a genetic switch controlling [Streptococcus pneumoniae](#) (the pneumococcus) that allows the bacterium to randomly change its characteristics into six alternative states that could pave the way to improved vaccines. Each form is randomly generated by a phase variable methylation system. The ability of the pneumococcus to cause deadly infections is different in each of these six states. Similar systems exist in other bacterial genera.^[190] In [Bacillota](#) such as [Clostridioides difficile](#), adenine methylation regulates [sporulation](#), [biofilm](#) formation and host-adaptation.^[191]

Medicine

[\[edit\]](#)

Epigenetics has many and varied potential medical applications.^[192]

Twins

[\[edit\]](#)

Direct comparisons of identical twins constitute an optimal model for interrogating [environmental epigenetics](#). In the case of humans with different environmental exposures, monozygotic (identical) twins were epigenetically indistinguishable during their

early years, while older twins had remarkable differences in the overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation.^[11] The twin pairs who had spent less of their lifetime together and/or had greater differences in their medical histories were those who showed the largest differences in their levels of [5-methylcytosine](#) DNA and [acetylation](#) of [histones](#) H3 and H4.^[193]

Dizygotic (fraternal) and monozygotic (identical) twins show evidence of epigenetic influence in humans.^{[193][194][195]} DNA sequence differences that would be abundant in a singleton-based study do not interfere with the analysis. Environmental differences can produce long-term epigenetic effects, and different developmental monozygotic twin subtypes may be different with respect to their susceptibility to be discordant from an epigenetic point of view.^[196]

A [high-throughput](#) study, which denotes technology that looks at extensive genetic markers, focused on epigenetic differences between monozygotic twins to compare global and locus-specific changes in [DNA methylation](#) and histone modifications in a sample of 40 monozygotic twin pairs.^[193] In this case, only healthy twin pairs were studied, but a wide range of ages was represented, between 3 and 74 years. One of the major conclusions from this study was that there is an age-dependent accumulation of epigenetic differences between the two siblings of twin pairs. This accumulation suggests the existence of epigenetic "drift". *Epigenetic drift* is the term given to epigenetic modifications as they occur as a direct function with age. While age is a known risk factor for many diseases, age-related methylation has been found to occur differentially at specific sites along the genome. Over time, this can result in measurable differences between biological and chronological age. Epigenetic changes have been found to be reflective of [lifestyle](#) and may act as functional [biomarkers](#) of disease before clinical [threshold](#) is reached.^[197]

A more recent study, where 114 monozygotic twins and 80 dizygotic twins were analyzed for the DNA methylation status of around 6000 unique genomic regions, concluded that epigenetic similarity at the time of blastocyst splitting may also contribute to phenotypic similarities in monozygotic co-twins. This supports the notion that [microenvironment](#) at early stages of embryonic development can be quite important for the establishment of epigenetic marks.^[194] Congenital genetic disease is well understood and it is clear that epigenetics can play a role, for example, in the case of [Angelman syndrome](#) and [Prader–Willi syndrome](#). These are normal genetic diseases caused by gene deletions or inactivation of the genes but are unusually common because individuals are essentially [hemizygous](#) because of [genomic imprinting](#), and therefore a single gene knock out is sufficient to cause the disease, where most cases would require both copies to be knocked out.^[198]

Genomic imprinting

[\[edit\]](#)

Further information: [Genomic imprinting](#)

Some human disorders are associated with genomic imprinting, a phenomenon in mammals where the father and mother contribute different epigenetic patterns for specific genomic loci in their [germ cells](#).^[199] The best-known case of imprinting in human disorders is that of [Angelman syndrome](#) and [Prader–Willi syndrome](#) – both can be produced by the same genetic mutation, [chromosome 15q partial deletion](#), and the particular syndrome that will develop depends on whether the mutation is inherited from the child's mother or from their father.^[200]

In the [Överkalix study](#), paternal (but not maternal) grandsons^[201] of Swedish men who were exposed during preadolescence to famine in the 19th century were less likely to die of cardiovascular disease. If food was plentiful, then [diabetes](#) mortality in the grandchildren increased, suggesting that this was a transgenerational epigenetic inheritance.^[202] The opposite effect was observed for females – the paternal (but not maternal) granddaughters of women who experienced famine while in the womb (and therefore while their eggs were being formed) lived shorter lives on average.^[203]

Examples of drugs altering gene expression from epigenetic events

[\[edit\]](#)

See also: [Epigenetic Priming](#)

The use of beta-lactam [antibiotics](#) can alter glutamate receptor activity and the action of cyclosporine on multiple transcription factors. Additionally, [lithium](#) can impact autophagy of aberrant proteins, and [opioid](#) drugs via chronic use can increase the expression of genes associated with addictive phenotypes. [\[204\]](#)

Parental [nutrition](#), in utero exposure to stress or [endocrine disrupting chemicals](#), [\[205\]](#) male-induced maternal effects such as the attraction of differential mate quality, and maternal as well as paternal age, and offspring gender could all possibly influence whether a germline epimutation is ultimately expressed in offspring and the degree to which intergenerational inheritance remains stable throughout posterity. [\[206\]](#) However, whether and to what extent epigenetic effects can be transmitted across generations remains unclear, particularly in humans. [\[207\]](#)[\[208\]](#)

Addiction

[\[edit\]](#)

[Addiction](#) is a disorder of the brain's [reward system](#) which arises through [transcriptional](#) and neuroepigenetic mechanisms and occurs over time from chronically high levels of exposure to an addictive stimulus (e.g., morphine, cocaine, sexual intercourse, gambling). [\[209\]](#)[\[210\]](#)[\[211\]](#) Transgenerational epigenetic inheritance of addictive [phenotypes](#) has been noted to occur in preclinical studies. [\[212\]](#)[\[213\]](#) However, robust evidence in support of the persistence of epigenetic effects across multiple generations has yet to be established in humans; for example, an epigenetic effect of prenatal exposure to smoking that is observed in great-grandchildren who had not been exposed. [\[207\]](#)

Research

[\[edit\]](#)

The two forms of heritable information, namely genetic and epigenetic, are collectively called dual inheritance. Members of the APOBEC/AID family of [cytosine deaminases](#) may concurrently influence genetic and epigenetic inheritance using similar molecular mechanisms, and may be a point of crosstalk between these conceptually compartmentalized processes. [\[214\]](#)

[Fluoroquinolone](#) antibiotics induce epigenetic changes in [mammalian](#) cells through iron [chelation](#). This leads to epigenetic effects through inhibition of α -ketoglutarate-dependent [dioxygenases](#) that require [iron](#) as a co-factor. [\[215\]](#)

Various pharmacological agents are applied for the production of induced pluripotent stem cells (iPSC) or maintain the embryonic stem cell (ESC) phenotypic via epigenetic approach. Adult stem cells like bone marrow stem cells have also shown a potential to differentiate into cardiac competent cells when treated with G9a histone methyltransferase inhibitor BIX01294. [\[216\]](#)[\[217\]](#)

Cell plasticity, which is the adaptation of cells to stimuli without changes in their genetic code, requires epigenetic changes. These have been observed in cell plasticity in cancer cells during epithelial-to-mesenchymal transition [\[218\]](#) and also in immune cells, such as macrophages. [\[219\]](#) Interestingly, metabolic changes underlie these adaptations, since various metabolites play crucial roles in the chemistry of epigenetic marks. This includes for instance alpha-ketoglutarate, which is required for histone demethylation, and acetyl-Coenzyme A, which is required for histone acetylation.

Epigenome editing

[\[edit\]](#)

Main article: [Epigenome editing](#)

Epigenetic regulation of gene expression that could be altered or used in [epigenome editing](#) are or include [mRNA/lncRNA modification](#), [DNA methylation](#) modification and [histone modification](#).^{[220][221][222]}

CpG sites, SNPs and biological traits

[\[edit\]](#)

Methylation is a widely characterized mechanism of genetic regulation that can determine biological traits. However, strong experimental evidences correlate methylation patterns in SNPs as an important additional feature for the classical activation/inhibition epigenetic dogma. Molecular interaction data, supported by colocalization analyses, identify multiple nuclear regulatory pathways, linking sequence variation to disturbances in DNA methylation and molecular and phenotypic variation.^[223]

UBASH3B locus

[\[edit\]](#)

UBASH3B encodes a protein with tyrosine phosphatase activity, which has been previously linked to advanced neoplasia.^[224] SNP rs7115089 was identified as influencing DNA methylation and expression of this locus, as well as and Body Mass Index (BMI).^[223] In fact, SNP rs7115089 is strongly associated with BMI^[225] and with genetic variants linked to other cardiovascular and metabolic traits in GWASs.^{[226][227][228]} New studies suggesting *UBASH3B* as a potential mediator of adiposity and cardiometabolic disease.^[223] In addition, animal models demonstrated that *UBASH3B* expression is an indicator of caloric restriction that may drive programmed susceptibility to obesity and it is associated with other measures of adiposity in human peripheral blood.^[229]

NFKBIE locus

[\[edit\]](#)

SNP rs730775 is located in the first intron of *NFKBIE* and is a *cis* eQTL for *NFKBIE* in whole blood.^[223] Nuclear factor (NF)-κB inhibitor ε (*NFKBIE*) directly inhibits NF-κB1 activity and is significantly co-expressed with NF-κB1, also, it is associated with rheumatoid arthritis.^[230] Colocalization analysis supports that variants for the majority of the CpG sites in SNP rs730775 cause genetic variation at the *NFKBIE* locus which is suggestible linked to rheumatoid arthritis through *trans* acting regulation of DNA methylation by NF-κB.^[223]

FADS1 locus

[\[edit\]](#)

Fatty acid desaturase 1 (*FADS1*) is a key enzyme in the metabolism of fatty acids.^[231] Moreover, rs174548 in the *FADS1* gene shows increased correlation with DNA methylation in people with high abundance of CD8+ T cells.^[223] SNP rs174548 is strongly associated with concentrations of arachidonic acid and other metabolites in fatty acid metabolism,^{[232][233]} blood eosinophil counts.^[234] and inflammatory diseases such as asthma.^[235] Interaction results indicated a correlation between rs174548 and asthma, providing new insights about fatty acid metabolism in CD8+ T cells with immune phenotypes.^[223]



Pseudoscience

[\[edit\]](#)

As epigenetics is in the early stages of development as a science and is surrounded by [sensationalism](#) in the public media, [David Gorski](#) and geneticist [Adam Rutherford](#) have advised caution against the proliferation of false and [pseudoscientific](#) conclusions by [new age](#) authors making unfounded suggestions that a person's genes and health can be manipulated by [mind control](#). Misuse of the scientific term by [quack authors](#) has produced misinformation among the general public.^{[2][236]}

See also

[\[edit\]](#)

-  [Biology portal](#) 754
-  [Medicine portal](#) 755
- [Baldwin effect](#) 756
- [Behavioral epigenetics](#) 757
- [Biological effects of radiation on the epigenome](#) 758
- [Computational epigenetics](#) 759
- [Contribution of epigenetic modifications to evolution](#) 760
- [DAnCER database \(2010\)](#) 761
- [Epigenesis \(biology\)](#) 762
- [Epigenetics in forensic science](#) 763
- [Epigenetics of autoimmune disorders](#) 764
- [Epiphenotyping](#) 765
- [Epigenetic therapy](#) 766
- [Epigenetics of neurodegenerative diseases](#) 767
- [Genetics](#) 768
- [Lamarckism](#) 769
- [Nutriepigenomics](#) 770
- [Position-effect variegation](#) 771
- [Preformationism](#) 772
- [Somatic epitype](#) 773
- [Synthetic genetic array](#) 774
- [Sleep epigenetics](#) 775
- [Transcriptional memory](#) 776
- [Transgenerational epigenetic inheritance](#) 777

References

[\[edit\]](#)

1. [^] Dupont C, Armant DR, Brenner CA (September 2009). ["Epigenetics: definition, mechanisms and clinical perspective"](#). *Seminars in Reproductive Medicine*. **27** (5): 351–7. doi:[10.1055/s-0029-1237423](#). PMC [2791696](#). PMID [19711245](#). In the original sense of this definition, epigenetics referred to all molecular pathways modulating the expression of a genotype into a particular phenotype. Over the following years, with the rapid growth of genetics, the meaning of the word has gradually narrowed. Epigenetics has been defined and today is generally accepted as 'the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence.'
2. [^] Jump up to: [ⓘ] [Ⓘ] Rutherford A (19 July 2015). ["Beware the pseudo gene genes"](#). *The Guardian*. 789

3. [^ Deans C, Maggert KA \(April 2015\). "What do you mean, "epigenetic"?"](#). *Genetics*. **199** (4): 887–896. [doi:10.1534/genetics.114.173492](#). [PMC 4391566](#). [PMID 25855649](#). 790
791
4. [^ Sharma S, Kelly TK, Jones PA \(January 2010\). "Epigenetics in cancer"](#). *Carcinogenesis*. **31** (1): 27–36. [doi:10.1093/carcin/bqp220](#). [PMC 2802667](#). [PMID 19752007](#). 792
793
5. [^ Kanwal R, Gupta S \(April 2012\). "Epigenetic modifications in cancer"](#). *Clinical Genetics*. **81** (4): 303–311. [doi:10.1111/j.1399-0004.2011.01809.x](#). [PMC 3590802](#). [PMID 22082348](#). 794
795
6. [^ Frías-Lasserre D, Villagra CA \(2017\). "The Importance of ncRNAs as Epigenetic Mechanisms in Phenotypic Variation and Organic Evolution"](#). *Frontiers in Microbiology*. **8**: 2483. [doi:10.3389/fmicb.2017.02483](#). [PMC 5744636](#). [PMID 29312192](#). 796
797
798
7. [^ Jump up to: ^a ^b Bird A \(May 2007\). "Perceptions of epigenetics"](#). *Nature*. **447** (7143): 396–398. [Bibcode:2007Natur.447..396B](#). [doi:10.1038/nature05913](#). [PMID 17522671](#). [S2CID 4357965](#). 799
800
8. [^ Hunter P \(1 May 2008\). "What genes remember"](#). *Prospect Magazine*. Archived from [the original](#) on 1 May 2008. Retrieved 26 July 2012. 801
802
9. [^ Reik W \(May 2007\). "Stability and flexibility of epigenetic gene regulation in mammalian development"](#). *Nature*. **447** (7143): 425–429. [Bibcode:2007Natur.447..425R](#). [doi:10.1038/nature05918](#). [PMID 17522676](#). [S2CID 11794102](#). 803
804
805
10. [^ Oxford English Dictionary](#): "The word is used by W. Harvey, *Exercitationes* 1651, p. 148, and in the *English Anatomical Exercitationes* 1653, p. 272. It is explained to mean 'partium super-exorientium additamentum', 'the additament of parts budding one out of another'." 806
807
808
11. [^ Jump up to: ^a ^b Moore DS \(2015\). *The Developing Genome: An Introduction to Behavioral Epigenetics*. Oxford University Press. \[ISBN 978-0-19-992235-2\]\(#\). ^{\[page needed\]} 809
810](#)
12. [^ Jump up to: ^a ^b Berger SL, Kouzarides T, Shiekhhattar R, Shilatifard A \(April 2009\). "An operational definition of epigenetics"](#). *Genes & Development*. **23** (7): 781–795. [doi:10.1101/qad.1787609](#). [PMC 3959995](#). [PMID 19339683](#). 811
812
813
13. [^ Jump up to: ^a ^b "Overview"](#). *NIH Roadmap Epigenomics Project*. Archived from [the original](#) on 21 November 2019. Retrieved 7 December 2013. 814
815
14. [^ Morange M. La tentative de Nikolai Koltzoff \(Koltsov\) de lier génétique, embryologie et chimie physique, J. Biosciences. 2011. V. 36. P. 211-214](#) 816
817
15. [^ Waddington CH \(1942\). "The epigenotype". *Endeavour*. **1**: 18–20. "For the purpose of a study of inheritance, the relation between phenotypes and genotypes \[...\] is, from a wider biological point of view, of crucial importance, since it is the kernel of the whole problem of development."](#) 818
819
820
16. [^ See \[preformationism\]\(#\) for historical background. *Oxford English Dictionary*: "the theory that the germ is brought into existence \(by successive accretions\), and not merely developed, in the process of reproduction. \[...\] The opposite theory was formerly known as the 'theory of evolution'; to avoid the ambiguity of this name, it is now spoken of chiefly as the 'theory of preformation', sometimes as that of 'encasement' or 'emboîtement'."](#) 821
822
823
824
825
17. [^ Waddington CH \(2014\). *The Epigenetics of Birds*. Cambridge University Press. \[ISBN 978-1-107-44047-0\]\(#\). ^{\[page needed\]}](#) 826
827
18. [^ Hall BK \(January 2004\). "In search of evolutionary developmental mechanisms: the 30-year gap between 1944 and 1974"](#). *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*. **302** (1): 5–18. [Bibcode:2004JEZ...302....5H](#). [doi:10.1002/jez.b.20002](#). [PMID 14760651](#). 828
829
830
19. [^ Alvarez-Buylla ER, Chaos A, Aldana M, Benítez M, Cortes-Poza Y, Espinosa-Soto C, et al. \(3 November 2008\). "Floral morphogenesis: stochastic explorations of a gene network epigenetic landscape"](#). *PLOS* 831
832

- ONE. **3** (11):
e3626. [Bibcode:2008PLoSO...3.3626A](#). [doi:10.1371/journal.pone.0003626](#). [PMC 2572848](#). [PMID 18978941](#).
20. ^ Jump up to: [Rabajante JF, Babierra AL \(March 2015\). "Branching and oscillations in the epigenetic landscape of cell-fate determination". *Progress in Biophysics and Molecular Biology*. **117** \(2–3\): 240–249. \[doi:10.1016/j.pbiomolbio.2015.01.006\]\(#\). \[PMID 25641423\]\(#\). \[S2CID 2579314\]\(#\).](#)
 21. ^ Holliday R (January 1990). "[DNA methylation and epigenetic inheritance](#)". *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. **326** (1235): 329–38. [Bibcode:1990RSPTB.326..329H](#). [doi:10.1098/rstb.1990.0015](#). [PMID 1968668](#).
 22. ^ Jump up to: [Riggs AD, Martienssen RA, Russo VE \(1996\). *Epigenetic mechanisms of gene regulation*. Plainview, NY: Cold Spring Harbor Laboratory Press. pp. 1–4. \[ISBN 978-0-87969-490-6\]\(#\).^{\[page needed\]}](#)
 23. ^ Ledford H (October 2008). "[Language: Disputed definitions](#)". *Nature*. **455** (7216): 1023–8. [doi:10.1038/4551023a](#). [PMID 18948925](#).
 24. ^ Gibney ER, Nolan CM (July 2010). "[Epigenetics and gene expression](#)". *Heredity*. **105** (1): 4–13. [doi:10.1038/hdy.2010.54](#). [PMID 20461105](#). [S2CID 31611763](#).
 25. ^ Ptashne M (April 2007). "[On the use of the word 'epigenetic'](#)". *Current Biology*. **17** (7): R233–6. [Bibcode:2007CBio...17.R233P](#). [doi:10.1016/j.cub.2007.02.030](#). [PMID 17407749](#). [S2CID 17490277](#).
 26. ^ Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, et al. (October 2019). "[Metabolic regulation of gene expression by histone lactylation](#)". *Nature*. **574** (7779): 575–580. [Bibcode:2019Natur.574..575Z](#). [doi:10.1038/s41586-019-1678-1](#). [PMC 6818755](#). [PMID 31645732](#).
 27. ^ Kumar S, Chinnusamy V, Mohapatra T (2018). "[Epigenetics of Modified DNA Bases: 5-Methylcytosine and Beyond](#)". *Frontiers in Genetics*. **9**: 640. [doi:10.3389/fgene.2018.00640](#). [PMC 6305559](#). [PMID 30619465](#).
 28. ^ Greenberg MV, Bourc'his D (October 2019). "The diverse roles of DNA methylation in mammalian development and disease". *Nature Reviews. Molecular Cell Biology*. **20** (10): 590–607. [doi:10.1038/s41580-019-0159-6](#). [PMID 31399642](#). [S2CID 199512037](#).
 29. ^ Spitz F, Furlong EE (September 2012). "Transcription factors: from enhancer binding to developmental control". *Nat Rev Genet*. **13** (9): 613–26. [doi:10.1038/nrg3207](#). [PMID 22868264](#). [S2CID 205485256](#).
 30. ^ Jump up to: [Duke CG, Kennedy AJ, Gavin CF, Day JJ, Sweatt JD \(July 2017\). "\[Experience-dependent epigenomic reorganization in the hippocampus\]\(#\)". *Learn Mem*. **24** \(7\): 278–288. \[doi:10.1101/lm.045112.117\]\(#\). \[PMC 5473107\]\(#\). \[PMID 28620075\]\(#\).](#)
 31. ^ Jump up to: [Bernstein C \(2022\). "\[DNA Methylation and Establishing Memory\]\(#\)". *Epigenet Insights*. **15**: 25168657211072499. \[doi:10.1177/25168657211072499\]\(#\). \[PMC 8793415\]\(#\). \[PMID 35098021\]\(#\).](#)
 32. ^ Jump up to: [Rose NR, Klose RJ \(December 2014\). "\[Understanding the relationship between DNA methylation and histone lysine methylation\]\(#\)". *Biochim Biophys Acta*. **1839** \(12\): 1362–72. \[doi:10.1016/j.bbagr.2014.02.007\]\(#\). \[PMC 4316174\]\(#\). \[PMID 24560929\]\(#\).](#)
 33. ^ Jump up to: [Li Y, Chen X, Lu C \(May 2021\). "\[The interplay between DNA and histone methylation: molecular mechanisms and disease implications\]\(#\)". *EMBO Rep*. **22** \(5\): e51803. \[doi:10.15252/embr.202051803\]\(#\). \[PMC 8097341\]\(#\). \[PMID 33844406\]\(#\).](#)
 34. ^ Bendandi A, Patelli AS, Diaspro A, Rocchia W (2020). "[The role of histone tails in nucleosome stability: An electrostatic perspective](#)". *Comput Struct Biotechnol J*. **18**: 2799–2809. [doi:10.1016/j.csbj.2020.09.034](#). [PMC 7575852](#). [PMID 33133421](#).
 35. ^ Stewart MD, Li J, Wong J (April 2005). "[Relationship between histone H3 lysine 9 methylation, transcription repression, and heterochromatin protein 1 recruitment](#)". *Molecular and Cellular Biology*. **25** (7): 2525–2538. [doi:10.1128/MCB.25.7.2525-2538.2005](#). [PMC 1061631](#). [PMID 15767660](#).

36. [Khan FA \(2014\). "Genetic disorders and gene therapy". Biotechnology in Medical Sciences. pp. 264–289. doi:10.1201/b16905-14. ISBN 978-0-429-17411-7.](#) 876
877
37. [Jenuwein T, Laible G, Dorn R, Reuter G \(January 1998\). "SET domain proteins modulate chromatin domains in eu- and heterochromatin". Cellular and Molecular Life Sciences. 54 \(1\): 80–93. doi:10.1007/s000180050127. PMC 11147257. PMID 9487389. S2CID 7769686.](#) 878
879
880
38. [Slotkin RK, Martienssen R \(April 2007\). "Transposable elements and the epigenetic regulation of the genome". Nature Reviews. Genetics. 8 \(4\): 272–85. doi:10.1038/nrg2072. PMID 17363976. S2CID 9719784.](#) 881
882
39. [Jump up to: ^a ^b Li E, Bestor TH, Jaenisch R \(June 1992\). "Targeted mutation of the DNA methyltransferase gene results in embryonic lethality". Cell. 69 \(6\): 915–26. doi:10.1016/0092-8674\(92\)90611-F. PMID 1606615. S2CID 19879601.](#) 883
884
885
40. [Robertson KD, Uzvolgyi E, Liang G, Talmadge C, Sumegi J, Gonzales FA, et al. \(June 1999\). "The human DNA methyltransferases \(DNMTs\) 1, 3a and 3b: coordinate mRNA expression in normal tissues and overexpression in tumors". Nucleic Acids Research. 27 \(11\): 2291–8. doi:10.1093/nar/27.11.2291. PMC 148793. PMID 10325416.](#) 886
887
888
889
41. [Leonhardt H, Page AW, Weier HU, Bestor TH \(November 1992\). "A targeting sequence directs DNA methyltransferase to sites of DNA replication in mammalian nuclei" \(PDF\). Cell. 71 \(5\): 865–73. doi:10.1016/0092-8674\(92\)90561-P. PMID 1423634. S2CID 5995820.](#) 890
891
892
42. [Chuang LS, Ian HI, Koh TW, Ng HH, Xu G, Li BF \(September 1997\). "Human DNA-\(cytosine-5\) methyltransferase-PCNA complex as a target for p21WAF1". Science. 277 \(5334\): 1996–2000. doi:10.1126/science.277.5334.1996. PMID 9302295.](#) 893
894
895
43. [Robertson KD, Wolffe AP \(October 2000\). "DNA methylation in health and disease". Nature Reviews. Genetics. 1 \(1\): 11–9. doi:10.1038/35049533. PMID 11262868. S2CID 1915808.](#) 896
897
44. [Li E, Beard C, Jaenisch R \(November 1993\). "Role for DNA methylation in genomic imprinting". Nature. 366\(6453\): 362–5. Bibcode:1993Natur.366..362L. doi:10.1038/366362a0. PMID 8247133. S2CID 4311091.](#) 898
899
900
45. [Viens A, Mechold U, Brouillard F, Gilbert C, Leclerc P, Ogryzko V \(July 2006\). "Analysis of human histone H2AZ deposition in vivo argues against its direct role in epigenetic templating mechanisms". Molecular and Cellular Biology. 26 \(14\): 5325–35. doi:10.1128/MCB.00584-06. PMC 1592707. PMID 16809769.](#) 901
902
903
46. [Ogryzko VV \(April 2008\). "Erwin Schroedinger, Francis Crick and epigenetic stability". Biology Direct. 3: 15. doi:10.1186/1745-6150-3-15. PMC 2413215. PMID 18419815.](#) 904
905
47. [Barbieri I, Kouzarides T \(June 2020\). "Role of RNA modifications in cancer". Nature Reviews. Cancer. 20 \(6\): 303–322. doi:10.1038/s41568-020-0253-2. PMID 32300195.](#) 906
907
48. [Nottke A, Colaiácovo MP, Shi Y \(March 2009\). "Developmental roles of the histone lysine demethylases". Development. 136 \(6\): 879–89. doi:10.1242/dev.020966. PMC 2692332. PMID 19234061.](#) 908
909
49. [Rosenfeld JA, Wang Z, Schones DE, Zhao K, DeSalle R, Zhang MQ \(March 2009\). "Determination of enriched histone modifications in non-genic portions of the human genome". BMC Genomics. 10: 143. doi:10.1186/1471-2164-10-143. PMC 2667539. PMID 19335899.](#) 910
911
912
50. [Sneppen K, Micheelsen MA, Dodd IB \(15 April 2008\). "Ultrasensitive gene regulation by positive feedback loops in nucleosome modification". Molecular Systems Biology. 4 \(1\): 182. doi:10.1038/msb.2008.21. PMC 2387233. PMID 18414483.](#) 913
914
915
51. ["Epigenetic cell memory". Cmol.nbi.dk. Archived from the original on 30 September 2011. Retrieved 26 July 2012.](#) 916
917

52. [^ Dodd IB, Micheelsen MA, Sneppen K, Thon G \(May 2007\). "Theoretical analysis of epigenetic cell memory by nucleosome modification". *Cell*. **129** \(4\): 813–](#) 918
[22. doi:10.1016/j.cell.2007.02.053. PMID 17512413. S2CID 16091877.](#) 919
920
53. [^ Morris KL \(2008\). "Epigenetic Regulation of Gene Expression". *RNA and the Regulation of Gene Expression: A Hidden Layer of Complexity*. Norfolk, England: Caister Academic Press. ISBN 978-1-904455-25-7.^{\[page needed\]}](#) 921
922
54. [^ Mattick JS, Amaral PP, Dinger ME, Mercer TR, Mehler MF \(January 2009\). "RNA regulation of epigenetic processes". *BioEssays*. **31** \(1\): 51–9. doi:10.1002/bies.080099. PMID 19154003. S2CID 19293469.](#) 923
924
55. [^ Choi CQ \(25 May 2006\). "RNA can be hereditary molecule". *The Scientist*. Archived from the original on 8 February 2007.](#) 925
926
56. [^ Jump up to: ^a ^b ^c Wang Z, Yao H, Lin S, Zhu X, Shen Z, Lu G, et al. \(April 2013\). "Transcriptional and epigenetic regulation of human microRNAs". *Cancer Letters*. **331** \(1\): 1–](#) 927
[10. doi:10.1016/j.canlet.2012.12.006. PMID 23246373.](#) 928
929
57. [^ "Browse miRBase by species".](#) 930
58. [^ Lim LP, Lau NC, Garrett-Engele P, Grimson A, Schelter JM, Castle J, et al. \(February 2005\). "Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs". *Nature*. **433** \(7027\): 769–](#) 931
[73. Bibcode:2005Natur.433..769L. doi:10.1038/nature03315. PMID 15685193. S2CID 4430576.](#) 932
933
934
59. [^ Lee D, Shin C \(October 2012\). "MicroRNA-target interactions: new insights from genome-wide approaches". *Annals of the New York Academy of Sciences*. **1271** \(1\): 118–](#) 935
[28. Bibcode:2012NYASA1271..118L. doi:10.1111/j.1749-6632.2012.06745.x. PMC 3499661. PMID 23050973.](#) 936
937
60. [^ Friedman RC, Farh KK, Burge CB, Bartel DP \(January 2009\). "Most mammalian mRNAs are conserved targets of microRNAs". *Genome Research*. **19** \(1\): 92–](#) 938
[105. doi:10.1101/gr.082701.108. PMC 2612969. PMID 18955434.](#) 939
940
61. [^ Goll MG, Bestor TH \(2005\). "Eukaryotic cytosine methyltransferases". *Annual Review of Biochemistry*. **74**: 481–](#) 941
[514. doi:10.1146/annurev.biochem.74.010904.153721. PMID 15952895. S2CID 32123961.](#) 942
943
62. [^ Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, et al. \(October 2011\). "N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO". *Nature Chemical Biology*. **7** \(12\): 885–](#) 944
[7. doi:10.1038/nchembio.687. PMC 3218240. PMID 22002720.](#) 945
946
63. [^ "New research links common RNA modification to obesity". *Physorg.com*. Retrieved 26 July 2012.](#) 947
64. [^ Howden BP, Beaume M, Harrison PF, Hernandez D, Schrenzel J, Seemann T, et al. \(August 2013\). "Analysis of the small RNA transcriptional response in multidrug-resistant *Staphylococcus aureus* after antimicrobial exposure". *Antimicrobial Agents and Chemotherapy*. **57** \(8\): 3864–74. doi:10.1128/AAC.00263-13. PMC 3719707. PMID 23733475.](#) 948
949
950
951
65. [^ "sRNA TarBase 2.0 A comprehensive database of bacterial SRNA targets verified by experiments". Archived from the original on 26 September 2013.](#) 952
953
66. [^ "Genomics maps for small non-coding RNA's and their targets in microbial genomes". Archived from the original on 8 June 2017. Retrieved 13 August 2013.](#) 954
955
67. [^ Ruffo, Paola, et al. "Long-noncoding RNAs as epigenetic regulators in neurodegenerative diseases." *Neural Regeneration Research* 18.6 \(2023\): 1243.](#) 956
957
68. [^ Bresnahan ST, Lee E, Clark L, Ma R, Rangel J, Grozinger CM, et al. \(June 2023\). "Examining parent-of-origin effects on transcription and RNA methylation in mediating aggressive behavior in honey bees \(*Apis mellifera*\)". *BMC Genomics*. **24** \(1\): 315. doi:10.1186/s12864-023-09411-4. PMC 10258952. PMID 37308882.](#) 958
959
960

69. [Yool A, Edmunds WJ \(1998\). "Epigenetic inheritance and prions". *Journal of Evolutionary Biology*. **11** \(2\): 241–42. doi:10.1007/s000360050085.](#) 961
70. [Cox BS \(1965\). "\[PSI\], a cytoplasmic suppressor of super-suppression in yeast". *Heredity*. **20** \(4\): 505–21. doi:10.1038/hdy.1965.65.](#) 962
71. [Lacroute F \(May 1971\). "Non-Mendelian mutation allowing ureidosuccinic acid uptake in yeast". *Journal of Bacteriology*. **106** \(2\): 519–22. doi:10.1128/JB.106.2.519-522.1971. PMC 285125. PMID 5573734.](#) 963
72. [Liebman SW, Sherman F \(September 1979\). "Extrachromosomal psi+ determinant suppresses nonsense mutations in yeast". *Journal of Bacteriology*. **139** \(3\): 1068–71. doi:10.1128/JB.139.3.1068-1071.1979. PMC 218059. PMID 225301.](#) 964
73. [True HL, Lindquist SL \(September 2000\). "A yeast prion provides a mechanism for genetic variation and phenotypic diversity". *Nature*. **407** \(6803\): 477–83. Bibcode:2000Natur.407..477T. doi:10.1038/35035005. PMID 11028992. S2CID 4411231.](#) 965
74. [Shorter J, Lindquist S \(June 2005\). "Prions as adaptive conduits of memory and inheritance". *Nature Reviews. Genetics*. **6** \(6\): 435–50. doi:10.1038/nrg1616. PMID 15931169. S2CID 5575951.](#) 966
75. [Giacomelli MG, Hancock AS, Masel J \(February 2007\). "The conversion of 3' UTRs into coding regions". *Molecular Biology and Evolution*. **24** \(2\): 457–64. doi:10.1093/molbev/msl172. PMC 1808353. PMID 17099057.](#) 967
76. [Lancaster AK, Bardill JP, True HL, Masel J \(February 2010\). "The spontaneous appearance rate of the yeast prion \[PSI+\] and its implications for the evolution of the evolvability properties of the \[PSI+\] system". *Genetics*. **184** \(2\): 393–400. doi:10.1534/genetics.109.110213. PMC 2828720. PMID 19917766.](#) 968
77. [Garcia DM, Campbell EA, Jakobson CM, Tsuchiya M, Shaw EA, DiNardo AL, et al. \(September 2021\). "A prion accelerates proliferation at the expense of lifespan". *eLife*. **10**: e60917. doi:10.7554/eLife.60917. PMC 8455135. PMID 34545808.](#) 969
78. [Topart C, Werner E, Arimondo PB \(July 2020\). "Wandering along the epigenetic timeline". *Clin Epigenetics*. **12** \(1\): 97. doi:10.1186/s13148-020-00893-7. PMC 7330981. PMID 32616071.](#) 970
79. [Chandler VL \(February 2007\). "Paramutation: from maize to mice". *Cell*. **128** \(4\): 641–5. doi:10.1016/j.cell.2007.02.007. PMID 17320501. S2CID 6928707.](#) 971
80. [Zaidi SK, Lian JB, van Wijnen A, Stein JL, Stein GS \(2017\). "Mitotic Gene Bookmarking: An Epigenetic Mechanism for Coordination of Lineage Commitment, Cell Identity and Cell Growth". *RUNX Proteins in Development and Cancer. Advances in Experimental Medicine and Biology*. Vol. 962. pp. 95–102. doi:10.1007/978-981-10-3233-2_7. ISBN 978-981-10-3231-8. PMC 7233416. PMID 28299653.](#) 972
81. [Suter CM, Martin DI \(January 2010\). "Paramutation: the tip of an epigenetic iceberg?". *Trends in Genetics*. **26** \(1\): 9–14. doi:10.1016/j.tig.2009.11.003. PMC 3137459. PMID 19945764.](#) 973
82. [Ferguson-Smith AC \(July 2011\). "Genomic imprinting: the emergence of an epigenetic paradigm". *Nature Reviews. Genetics*. **12** \(8\): 565–575. doi:10.1038/nrg3032. PMID 21765458. S2CID 23630392.](#) 974
83. [Kovalchuk O, Baulch JE \(January 2008\). "Epigenetic changes and nontargeted radiation effects--is there a link?". *Environmental and Molecular Mutagenesis*. **49** \(1\): 16–25. Bibcode:2008EnvMM..49...16K. doi:10.1002/em.20361. PMID 18172877. S2CID 38705208.](#) 975
84. [Ilnytskyy Y, Kovalchuk O \(September 2011\). "Non-targeted radiation effects-an epigenetic connection". *Mutation Research*. **714** \(1–2\): 113–25. Bibcode:2011MRFMM.714..113I. doi:10.1016/j.mrfmmm.2011.06.014. PMID 21784089.](#) 976

85. [Friedl AA, Mazurek B, Seiler DM \(2012\). "Radiation-induced alterations in histone modification patterns and their potential impact on short-term radiation effects". Frontiers in Oncology. 2: 117. doi:10.3389/fonc.2012.00117. PMC 3445916. PMID 23050241.](#) 1002
1003
1004
86. [Cuozzo C, Porcellini A, Angrisano T, Morano A, Lee B, Di Pardo A, et al. \(July 2007\). "DNA damage, homology-directed repair, and DNA methylation". PLOS Genetics. 3 \(7\): e110. doi:10.1371/journal.pgen.0030110. PMC 1913100. PMID 17616978.](#) 1005
1006
1007
87. [O'Hagan HM, Mohammad HP, Baylin SB \(August 2008\). Lee JT \(ed.\). "Double strand breaks can initiate gene silencing and SIRT1-dependent onset of DNA methylation in an exogenous promoter CpG island". PLOS Genetics. 4 \(8\): e1000155. doi:10.1371/journal.pgen.1000155. PMC 2491723. PMID 18704159.](#) 1008
1009
1010
88. [Malanga M, Althaus FR \(June 2005\). "The role of poly\(ADP-ribose\) in the DNA damage signaling network"\(PDF\). Biochemistry and Cell Biology. 83 \(3\): 354–64. doi:10.1139/o05-038. PMID 15959561.](#) 1011
1012
89. [Gottschalk AJ, Timinszky G, Kong SE, Jin J, Cai Y, Swanson SK, et al. \(August 2009\). "Poly\(ADP-ribosyl\)ation directs recruitment and activation of an ATP-dependent chromatin remodeler". Proceedings of the National Academy of Sciences of the United States of America. 106 \(33\): 13770–4. Bibcode:2009PNAS..10613770G. doi:10.1073/pnas.0906920106. PMC 2722505. PMID 19666485.](#) 1013
1014
1015
1016
90. [Lin JC, Jeong S, Liang G, Takai D, Fatemi M, Tsai YC, et al. \(November 2007\). "Role of nucleosomal occupancy in the epigenetic silencing of the MLH1 CpG island". Cancer Cell. 12 \(5\): 432–44. doi:10.1016/j.ccr.2007.10.014. PMC 4657456. PMID 17996647.](#) 1017
1018
1019
91. [Tabish AM, Poels K, Hoet P, Godderis L \(2012\). Chiariotti L \(ed.\). "Epigenetic factors in cancer risk: effect of chemical carcinogens on global DNA methylation pattern in human TK6 cells". PLOS ONE. 7 \(4\): e34674. Bibcode:2012PLoSO...734674T. doi:10.1371/journal.pone.0034674. PMC 3324488. PMID 22509344.](#) 1020
1021
1022
92. [Burdge GC, Hoile SP, Uller T, Thomas NA, Gluckman PD, Hanson MA, et al. \(2011\). Imhof A \(ed.\). "Progressive, transgenerational changes in offspring phenotype and epigenotype following nutritional transition". PLOS ONE. 6 \(11\): e28282. Bibcode:2011PLoSO...628282B. doi:10.1371/journal.pone.0028282. PMC 3227644. PMID 22140567.](#) 1023
1024
1025
1026
93. [Fang M, Chen D, Yang CS \(January 2007\). "Dietary polyphenols may affect DNA methylation". The Journal of Nutrition. 137 \(1 Suppl\): 223S – 228S. doi:10.1093/jn/137.1.223S. PMID 17182830.](#) 1027
1028
94. [Olaharski AJ, Rine J, Marshall BL, Babiarz J, Zhang L, Verdin E, et al. \(December 2005\). "The flavoring agent dihydrocoumarin reverses epigenetic silencing and inhibits sirtuin deacetylases". PLOS Genetics. 1 \(6\): e77. doi:10.1371/journal.pgen.0010077. PMC 1315280. PMID 16362078.](#) 1029
1030
1031
95. [Djuric Z, Chen G, Doerge DR, Heilbrun LK, Kucuk O \(October 2001\). "Effect of soy isoflavone supplementation on markers of oxidative stress in men and women". Cancer Letters. 172 \(1\): 1–6. doi:10.1016/S0304-3835\(01\)00627-9. PMID 11595123.](#) 1032
1033
1034
96. [Kropat C, Mueller D, Boettler U, Zimmermann K, Heiss EH, Dirsch VM, et al. \(March 2013\). "Modulation of Nrf2-dependent gene transcription by bilberry anthocyanins in vivo". Molecular Nutrition & Food Research. 57\(3\): 545–50. doi:10.1002/mnfr.201200504. PMID 23349102.](#) 1035
1036
1037
97. [Swenberg JA, Lu K, Moeller BC, Gao L, Upton PB, Nakamura J, et al. \(March 2011\). "Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment". Toxicol Sci. 120\(Suppl 1\): S130–45. doi:10.1093/toxsci/kfq371. PMC 3043087. PMID 21163908.](#) 1038
1039
1040
98. [Jump up to: ^a ^b Hamilton ML, Guo Z, Fuller CD, Van Remmen H, Ward WF, Austad SN, et al. \(May 2001\). "A reliable assessment of 8-oxo-2-deoxyguanosine levels in nuclear and mitochondrial DNA using the sodium iodide method to isolate DNA". Nucleic Acids Res. 29 \(10\): 2117–26. doi:10.1093/nar/29.10.2117. PMC 55450. PMID 11353081.](#) 1041
1042
1043
1044

99. [^ Ming X, Matter B, Song M, Veliath E, Shanley R, Jones R, et al. \(March 2014\). "Mapping structurally defined guanine oxidation products along DNA duplexes: influence of local sequence context and endogenous cytosine methylation". J Am Chem Soc. **136** \(11\): 4223–](#) 1045
[35. Bibcode:2014JChS.136.4223M. doi:10.1021/ja411636j. PMC 3985951. PMID 24571128.](#) 1046
[1171. doi:10.1016/j.celsiq.2016.05.021. PMID 27251462.](#) 1047
100. [^ Jump up to: ^{a b c} Zhou X, Zhuang Z, Wang W, He L, Wu H, Cao Y, et al. \(September 2016\). "OGG1 is essential in oxidative stress-induced DNA demethylation". Cell Signal. **28** \(9\): 1163–](#) 1048
[1171. doi:10.1016/j.celsiq.2016.05.021. PMID 27251462.](#) 1049
101. [^ Poetsch AR \(2020\). "The genomics of oxidative DNA damage, repair, and resulting mutagenesis". Comput Struct Biotechnol J. **18**: 207–](#) 1050
[219. doi:10.1016/j.csbj.2019.12.013. PMC 6974700. PMID 31993111.](#) 1051
102. [^ D'Augustin O, Huet S, Campalans A, Radicella JP \(November 2020\). "Lost in the Crowd: How Does Human 8-Oxoguanine DNA Glycosylase 1 \(OGG1\) Find 8-Oxoguanine in the Genome?". Int J Mol Sci. **21** \(21\):](#) 1052
[8360. doi:10.3390/ijms21218360. PMC 7664663. PMID 33171795.](#) 1053
103. [^ Lan L, Nakajima S, Oohata Y, Takao M, Okano S, Masutani M, et al. \(September 2004\). "In situ analysis of repair processes for oxidative DNA damage in mammalian cells". Proc Natl Acad Sci U S A. **101** \(38\): 13738–](#) 1054
[43. Bibcode:2004PNAS..10113738L. doi:10.1073/pnas.0406048101. PMC 518826. PMID 15365186.](#) 1055
104. [^ Maeder ML, Angstman JF, Richardson ME, Linder SJ, Cascio VM, Tsai SQ, et al. \(December 2013\). "Targeted DNA demethylation and activation of endogenous genes using programmable TALE-TET1 fusion proteins". Nat. Biotechnol. **31** \(12\): 1137–42. doi:10.1038/nbt.2726. PMC 3858462. PMID 24108092.](#) 1056
[1171. doi:10.1038/nbt.2726. PMC 3858462. PMID 24108092.](#) 1057
105. [^ Ding N, Bonham EM, Hannon BE, Amick TR, Baylin SB, O'Hagan HM \(June 2016\). "Mismatch repair proteins recruit DNA methyltransferase 1 to sites of oxidative DNA damage". J Mol Cell Biol. **8** \(3\): 244–](#) 1058
[54. doi:10.1093/jmcb/mjv050. PMC 4937888. PMID 26186941.](#) 1059
106. [^ Jump up to: ^{a b c} Jiang Z, Lai Y, Beaver JM, Tsegay PS, Zhao ML, Horton JK, et al. \(January 2020\). "Oxidative DNA Damage Modulates DNA Methylation Pattern in Human Breast Cancer 1 \(BRCA1\) Gene via the Crosstalk between DNA Polymerase \$\beta\$ and a de novo DNA Methyltransferase". Cells. **9** \(1\):](#) 1060
[225. doi:10.3390/cells9010225. PMC 7016758. PMID 31963223.](#) 1061
107. [^ Mortusewicz O, Schermelleh L, Walter J, Cardoso MC, Leonhardt H \(June 2005\). "Recruitment of DNA methyltransferase I to DNA repair sites". Proc Natl Acad Sci U S A. **102** \(25\): 8905–](#) 1062
[9. Bibcode:2005PNAS..102.8905M. doi:10.1073/pnas.0501034102. PMC 1157029. PMID 15956212.](#) 1063
108. [^ Jump up to: ^{a b c} Cuzzo C, Porcellini A, Angrisano T, Morano A, Lee B, Di Pardo A, et al. \(July 2007\). "DNA damage, homology-directed repair, and DNA methylation". PLOS Genet. **3** \(7\):](#) 1064
[e110. doi:10.1371/journal.pgen.0030110. PMC 1913100. PMID 17616978.](#) 1065
109. [^ Jump up to: ^{a b c} O'Hagan HM, Mohammad HP, Baylin SB \(August 2008\). "Double strand breaks can initiate gene silencing and SIRT1-dependent onset of DNA methylation in an exogenous promoter CpG island". PLOS Genet. **4** \(8\): e1000155. doi:10.1371/journal.pgen.1000155. PMC 2491723. PMID 18704159.](#) 1066
[1171. doi:10.1371/journal.pgen.1000155. PMC 2491723. PMID 18704159.](#) 1067
110. [^ Ha K, Lee GE, Palii SS, Brown KD, Takeda Y, Liu K, et al. \(January 2011\). "Rapid and transient recruitment of DNMT1 to DNA double-strand breaks is mediated by its interaction with multiple components of the DNA damage response machinery". Hum Mol Genet. **20** \(1\): 126–](#) 1068
[40. doi:10.1093/hmg/ddq451. PMC 3000680. PMID 20940144.](#) 1069
111. [^ Russo G, Landi R, Pezone A, Morano A, Zuchegna C, Romano A, et al. \(September 2016\). "DNA damage and Repair Modify DNA methylation and Chromatin Domain of the Targeted Locus: Mechanism of](#) 1070
[1171. doi:10.1093/hmg/ddq451. PMC 3000680. PMID 20940144.](#) 1071

- [allele methylation polymorphism". Sci Rep. 6: 33222. Bibcode:2016NatSR...633222R. doi:10.1038/srep33222. PMC 5024116. PMID 27629060.](#)
112. [^ Farris MH, Texter PA, Mora AA, Wiles MV, Mac Garrigle EF, Klaus SA, et al. \(December 2020\). "Detection of CRISPR-mediated genome modifications through altered methylation patterns of CpG islands". BMC Genomics. 21 \(1\): 856. doi:10.1186/s12864-020-07233-2. PMC 7709351. PMID 33267773.](#)
113. [^ Allen B, Pezone A, Porcellini A, Muller MT, Masternak MM \(June 2017\). "Non-homologous end joining induced alterations in DNA methylation: A source of permanent epigenetic change". Oncotarget. 8 \(25\): 40359–40372. doi:10.18632/oncotarget.16122. PMC 5522286. PMID 28423717.](#)
114. [^ Jump up to: ^{a b} Verma M, Rogers S, Divi RL, Schully SD, Nelson S, Joseph Su L, et al. \(February 2014\). "Epigenetic research in cancer epidemiology: trends, opportunities, and challenges". Cancer Epidemiology, Biomarkers & Prevention. 23 \(2\): 223–33. doi:10.1158/1055-9965.EPI-13-0573. PMC 3925982. PMID 24326628.](#)
115. [^ Jump up to: ^{a b} "Studying epigenetics using ChIP". Abcam.](#)
116. [^ Jump up to: ^{a b} Chaumeil J, Augui S, Chow JC, Heard E \(2008\). "Combined Immunofluorescence, RNA Fluorescent in Situ Hybridization, and DNA Fluorescent in Situ Hybridization to Study Chromatin Changes, Transcriptional Activity, Nuclear Organization, and X-Chromosome Inactivation". The Nucleus. Methods in Molecular Biology. Vol. 463. Clifton, N.J.: Springer. pp. 297–308. doi:10.1007/978-1-59745-406-3_18. ISBN 978-1-58829-977-2. PMID 18951174.](#)
117. [^ Jump up to: ^{a b} O'Connor C \(2008\). "Fluorescence in situ hybridization \(FISH\)". Nature Education. 1 \(1\): 171.](#)
118. [^ Jump up to: ^{a b c d} Hashimoto K, Kokubun S, Itoi E, Roach HI \(2007\). "Improved quantification of DNA methylation using methylation-sensitive restriction enzymes and real-time PCR". Epigenetics. 2 \(2\): 86–91. doi:10.4161/epi.2.2.4203. PMID 17965602. S2CID 26728480.](#)
119. [^ Li-Byarlay H, Boncristiani H, Howell G, Herman J, Clark L, Strand MK, et al. \(24 September 2020\). "Transcriptomic and Epigenomic Dynamics of Honey Bees in Response to Lethal Viral Infection". Frontiers in Genetics. 11: 566320. doi:10.3389/fgene.2020.566320. PMC 7546774. PMID 33101388.](#)
120. [^ Li-Byarlay H, Li Y, Stroud H, Feng S, Newman TC, Kaneda M, et al. \(July 2013\). "RNA interference knockdown of DNA methyl-transferase 3 affects gene alternative splicing in the honey bee". Proceedings of the National Academy of Sciences of the United States of America. 110 \(31\): 12750–12755. Bibcode:2013PNAS..11012750L. doi:10.1073/pnas.1310735110. PMC 3732956. PMID 23852726.](#)
121. [^ Simpson JT, Workman RE, Zuzarte PC, David M, Dursi LJ, Timp W \(April 2017\). "Detecting DNA cytosine methylation using nanopore sequencing". Nature Methods. 14 \(4\): 407–410. doi:10.1038/nmeth.4184. PMID 28218898. S2CID 16152628.](#)
122. [^ Sapp J \(1991\). "Concepts of Organization the Leverage of Ciliate Protozoa". A Conceptual History of Modern Embryology. Developmental Biology. Vol. 7. pp. 229–258. doi:10.1007/978-1-4615-6823-0_11. ISBN 978-1-4615-6825-4. PMID 1804215.](#)
123. [^ Sapp J \(2003\). Genesis: the evolution of biology. Oxford: Oxford University Press. ISBN 978-0-19-515619-5.](#)
124. [^ Gray RD, Oyama S, Griffiths PE \(2003\). Cycles of Contingency: Developmental Systems and Evolution \(Life and Mind: Philosophical Issues in Biology and Psychology\). Cambridge, Massachusetts: The MIT Press. ISBN 978-0-262-65063-2.](#)

125. [^ Serizay J, Dong Y, Jänes J, Chesney M, Cerrato C, Ahringer J \(20 February 2020\). "Tissue-specific profiling reveals distinctive regulatory architectures for ubiquitous, germline and somatic genes". bioRxiv: 2020.02.20.958579. doi:10.1101/2020.02.20.958579. S2CID 212943176.](#) 1130
1131
1132
126. [^ Jump up to: ^a Teif VB, Beshnova DA, Vainshtein Y, Marth C, Mallm JP, Höfer T, et al. \(August 2014\). "Nucleosome repositioning links DNA \(de\)methylation and differential CTCF binding during stem cell development". Genome Research. **24** \(8\): 1285–95. doi:10.1101/gr.164418.113. PMC 4120082. PMID 24812327.](#) 1133
1134
1135
1136
127. [^ Buschbeck M, Hake SB \(May 2017\). "Variants of core histones and their roles in cell fate decisions, development and cancer". Nature Reviews. Molecular Cell Biology. **18** \(5\): 299–314. doi:10.1038/nrm.2016.166. PMID 28144029. S2CID 3307731.](#) 1137
1138
1139
128. [^ Jang CW, Shibata Y, Starmer J, Yee D, Magnuson T \(July 2015\). "Histone H3.3 maintains genome integrity during mammalian development". Genes & Development. **29** \(13\): 1377–92. doi:10.1101/gad.264150.115. PMC 4511213. PMID 26159997.](#) 1140
1141
1142
129. [^ "The 3D genome". www.nature.com. 2 September 2019. Retrieved 26 September 2021.](#) 1143
130. [^ Kitamura T, Ogawa SK, Roy DS, Okuyama T, Morrissey MD, Smith LM, et al. \(April 2017\). "Engrams and circuits crucial for systems consolidation of a memory". Science. **356** \(6333\): 73–78. Bibcode:2017Sci...356...73K. doi:10.1126/science.aam6808. PMC 5493329. PMID 28386011.](#) 1144
1145
1146
131. [^ Jump up to: ^a Stott RT, Kritsky O, Tsai LH \(2021\). "Profiling DNA break sites and transcriptional changes in response to contextual fear learning". PLOS ONE. **16** \(7\): e0249691. Bibcode:2021PLoSO..1649691S. doi:10.1371/journal.pone.0249691. PMC 8248687. PMID 34197463.](#) 1147
1148
1149
1150
132. [^ Lee BH, Shim JY, Moon HC, Kim DW, Kim J, Yook JS, et al. \(July 2022\). "Real-time visualization of mRNA synthesis during memory formation in live mice". Proc Natl Acad Sci U S A. **119** \(27\): e2117076119. Bibcode:2022PNAS..11917076L. doi:10.1073/pnas.2117076119. PMC 9271212. PMID 35776545.](#) 1151
1152
1153
1154
133. [^ Tischmeyer W, Grimm R \(April 1999\). "Activation of immediate early genes and memory formation". Cell Mol Life Sci. **55** \(4\): 564–74. doi:10.1007/s000180050315. PMC 11146814. PMID 10357227. S2CID 6923522.](#) 1155
1156
1157
134. [^ Jump up to: ^a Oliveira AM, Hemstedt TJ, Bading H \(July 2012\). "Rescue of aging-associated decline in Dnmt3a2 expression restores cognitive abilities". Nat Neurosci. **15** \(8\): 1111–3. doi:10.1038/nn.3151. PMID 22751036. S2CID 10590208.](#) 1158
1159
1160
135. [^ Jump up to: ^a Sun Z, Xu X, He J, Murray A, Sun MA, Wei X, et al. \(August 2019\). "EGR1 recruits TET1 to shape the brain methylome during development and upon neuronal activity". Nat Commun. **10** \(1\): 3892. Bibcode:2019NatCo..10.3892S. doi:10.1038/s41467-019-11905-3. PMC 6715719. PMID 31467272.](#) 1161
1162
1163
136. [^ Manzo M, Wirz J, Ambrosi C, Villaseñor R, Roschitzki B, Baubec T \(December 2017\). "Isoform-specific localization of DNMT3A regulates DNA methylation fidelity at bivalent CpG islands". EMBO J. **36** \(23\): 3421–3434. doi:10.15252/embj.201797038. PMC 5709737. PMID 29074627.](#) 1164
1165
1166
137. [^ Joels G, Lamprecht R \(2014\). "Fear memory formation can affect a different memory: fear conditioning affects the extinction, but not retrieval, of conditioned taste aversion \(CTA\) memory". Front Behav Neurosci. **8**: 324. doi:10.3389/fnbeh.2014.00324. PMC 4179742. PMID 25324744.](#) 1167
1168
1169
138. [^ Moore LD, Le T, Fan G \(January 2013\). "DNA methylation and its basic function". Neuropsychopharmacology. **38** \(1\): 23–38. doi:10.1038/npp.2012.112. PMC 3521964. PMID 22781841.](#) 1170
1171
1172

139. ^ Jump up to: ²² Halder R, Hennion M, Vidal RO, Shomroni O, Rahman RU, Rajput A, et al. (January 2016). "DNA methylation changes in plasticity genes accompany the formation and maintenance of memory". *Nat Neurosci.* **19** (1): 102–10. [doi:10.1038/nn.4194](https://doi.org/10.1038/nn.4194). [PMID 26656643](https://pubmed.ncbi.nlm.nih.gov/26656643/). [S2CID 1173959](https://pubmed.ncbi.nlm.nih.gov/26656643/). 1173 1174 1175
140. ^ Frankland PW, Bontempi B, Talton LE, Kaczmarek L, Silva AJ (May 2004). "The involvement of the anterior cingulate cortex in remote contextual fear memory". *Science.* **304** (5672): 881– 1176 1177 1178
3. [Bibcode:2004Sci...304..881F](https://pubmed.ncbi.nlm.nih.gov/15131309/). [doi:10.1126/science.1094804](https://doi.org/10.1126/science.1094804). [PMID 15131309](https://pubmed.ncbi.nlm.nih.gov/15131309/). [S2CID 15893863](https://pubmed.ncbi.nlm.nih.gov/15131309/). 1178
141. ^ Barter JD, Foster TC (October 2018). "Aging in the Brain: New Roles of Epigenetics in Cognitive Decline". *The Neuroscientist.* **24** (5): 516– 1179 1180 1181
525. [doi:10.1177/1073858418780971](https://doi.org/10.1177/1073858418780971). [PMID 29877135](https://pubmed.ncbi.nlm.nih.gov/29877135/). [S2CID 46965080](https://pubmed.ncbi.nlm.nih.gov/29877135/). 1181
142. ^ Harman MF, Martín MG (February 2020). "Epigenetic mechanisms related to cognitive decline during aging". *Journal of Neuroscience Research.* **98** (2): 234– 1182 1183 1184
246. [doi:10.1002/jnr.24436](https://doi.org/10.1002/jnr.24436). [PMID 31045277](https://pubmed.ncbi.nlm.nih.gov/31045277/). [S2CID 143423862](https://pubmed.ncbi.nlm.nih.gov/31045277/). 1184
143. ^ Braga DL, Mousovich-Neto F, Tonon-da-Silva G, Salgueiro WG, Mori MA (August 2020). "Epigenetic changes during ageing and their underlying mechanisms". *Biogerontology.* **21** (4): 423– 1185 1186 1187
443. [doi:10.1007/s10522-020-09874-y](https://doi.org/10.1007/s10522-020-09874-y). [PMID 32356238](https://pubmed.ncbi.nlm.nih.gov/32356238/). [S2CID 254292058](https://pubmed.ncbi.nlm.nih.gov/32356238/). 1187
144. ^ Zhang W, Qu J, Liu GH, Belmonte JC (March 2020). "The ageing epigenome and its rejuvenation". *Nature Reviews. Molecular Cell Biology.* **21** (3): 137–150. [doi:10.1038/s41580-019-0204-5](https://doi.org/10.1038/s41580-019-0204-5). [PMID 32020082](https://pubmed.ncbi.nlm.nih.gov/32020082/). [S2CID 211028527](https://pubmed.ncbi.nlm.nih.gov/32020082/). 1188 1189 1190
145. ^ Simpson DJ, Olova NN, Chandra T (September 2021). "[Cellular reprogramming and epigenetic rejuvenation](https://pubmed.ncbi.nlm.nih.gov/34488874/)". *Clinical Epigenetics.* **13** (1): 170. [doi:10.1186/s13148-021-01158-7](https://doi.org/10.1186/s13148-021-01158-7). [PMC 8419998](https://pubmed.ncbi.nlm.nih.gov/34488874/). [PMID 34488874](https://pubmed.ncbi.nlm.nih.gov/34488874/). 1191 1192 1193
146. ^ Hwang JY, Aromolaran KA, Zukin RS (May 2017). "[The emerging field of epigenetics in neurodegeneration and neuroprotection](https://pubmed.ncbi.nlm.nih.gov/28515491/)". *Nature Reviews. Neuroscience.* **18** (6): 347– 1194 1195 1196
361. [doi:10.1038/nrn.2017.46](https://doi.org/10.1038/nrn.2017.46). [PMC 6380351](https://pubmed.ncbi.nlm.nih.gov/28515491/). [PMID 28515491](https://pubmed.ncbi.nlm.nih.gov/28515491/). 1196
147. ^ Grigorenko EL, Kornilov SA, Naumova OY (November 2016). "Epigenetic regulation of cognition: A circumscribed review of the field". *Development and Psychopathology.* **28** (4pt2): 1285– 1197 1198 1199
1304. [doi:10.1017/S0954579416000857](https://doi.org/10.1017/S0954579416000857). [PMID 27691982](https://pubmed.ncbi.nlm.nih.gov/27691982/). [S2CID 21422752](https://pubmed.ncbi.nlm.nih.gov/27691982/). 1199
148. ^ Bacon ER, Brinton RD (June 2021). "[Epigenetics of the developing and aging brain: Mechanisms that regulate onset and outcomes of brain reorganization](https://pubmed.ncbi.nlm.nih.gov/33657435/)". *Neuroscience and Biobehavioral Reviews.* **125**: 503–516. [doi:10.1016/j.neubiorev.2021.02.040](https://doi.org/10.1016/j.neubiorev.2021.02.040). [PMC 8989071](https://pubmed.ncbi.nlm.nih.gov/33657435/). [PMID 33657435](https://pubmed.ncbi.nlm.nih.gov/33657435/). 1200 1201 1202
149. ^ Streifer M, Gore AC (2021). "Epigenetics, estrogenic endocrine-disrupting chemicals (EDCs), and the brain". *Endocrine-Disrupting Chemicals. Advances in Pharmacology.* Vol. 92. pp. 73– 1203 1204 1205
99. [doi:10.1016/bs.apha.2021.03.006](https://doi.org/10.1016/bs.apha.2021.03.006). [ISBN 9780128234662](https://pubmed.ncbi.nlm.nih.gov/34452697/). [PMID 34452697](https://pubmed.ncbi.nlm.nih.gov/34452697/). [S2CID 237339845](https://pubmed.ncbi.nlm.nih.gov/34452697/). 1205
150. ^ Bekdash RA (January 2018). "Choline, the brain and neurodegeneration: insights from epigenetics". *Frontiers in Bioscience.* **23** (6): 1113–1143. [doi:10.2741/4636](https://doi.org/10.2741/4636). [PMID 28930592](https://pubmed.ncbi.nlm.nih.gov/28930592/). 1206 1207
151. ^ Ekstrand B, Scheers N, Rasmussen MK, Young JF, Ross AB, Landberg R (May 2021). "Brain foods - the role of diet in brain performance and health". *Nutrition Reviews.* **79** (6): 693– 1208 1209 1210
708. [doi:10.1093/nutrit/nuaa091](https://doi.org/10.1093/nutrit/nuaa091). [PMID 32989449](https://pubmed.ncbi.nlm.nih.gov/32989449/). 1210
152. ^ Fernandes J, Arida RM, Gomez-Pinilla F (September 2017). "[Physical exercise as an epigenetic modulator of brain plasticity and cognition](https://pubmed.ncbi.nlm.nih.gov/28666827/)". *Neuroscience and Biobehavioral Reviews.* **80**: 443– 1211 1212 1213
456. [doi:10.1016/j.neubiorev.2017.06.012](https://doi.org/10.1016/j.neubiorev.2017.06.012). [PMC 5705447](https://pubmed.ncbi.nlm.nih.gov/28666827/). [PMID 28666827](https://pubmed.ncbi.nlm.nih.gov/28666827/). 1213
153. ^ Tamim B (4 September 2022). "[New discovery: Synapse hiding in the mice brain may advance our understanding of neuronal communication](https://pubmed.ncbi.nlm.nih.gov/32989449/)". *interestingengineering.com*. Retrieved 19 October 2022. 1214 1215

154. [Sheu SH, Upadhyayula S, Dupuy V, Pang S, Deng F, Wan J, et al. \(September 2022\). "A serotonergic axon-cilium synapse drives nuclear signaling to alter chromatin accessibility". Cell. **185** \(18\): 3390–3407.e18. doi:10.1016/j.cell.2022.07.026. PMC 9789380. PMID 36055200. S2CID 251958800.](#) 1216
 - University press release: ["Scientists discover new kind of synapse in neurons' tiny hairs"](#). Howard Hughes Medical Institute via phys.org. Retrieved 19 October 2022. 1217
1218
155. [Keverne EB \(April 2011\). "Epigenetics and brain evolution". Epigenomics. **3** \(2\): 183–191. doi:10.2217/epi.11.10. PMID 22122280.](#) 1221
1222
156. [Griesemer J, Haber MH, Yamashita G, Gannett L \(March 2005\). "Critical Notice: Cycles of Contingency – Developmental Systems and Evolution". Biology & Philosophy. **20** \(2–3\): 517–44. doi:10.1007/s10539-004-0836-4. S2CID 2995306.](#) 1223
1224
1225
157. [Chapter: "Nervous System Development" in "Epigenetics," by Benedikt Hallgrímsson and Brian Hall](#) 1226
158. [Costa S, Shaw P \(March 2007\). "'Open minded' cells: how cells can change fate" \(PDF\). Trends in Cell Biology. **17** \(3\): 101–6. doi:10.1016/j.tcb.2006.12.005. PMID 17194589. Archived from the original\(PDF\) on 15 December 2013. This might suggest that plant cells do not use or require a cellular memory mechanism and just respond to positional information. However, it has been shown that plants do use cellular memory mechanisms mediated by PcG proteins in several processes, ... \(p. 104\)](#) 1227
1228
1229
1230
1231
159. [Cooney CA, Dave AA, Wolff GL \(August 2002\). "Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring". The Journal of Nutrition. **132** \(8 Suppl\): 2393S – 2400S. doi:10.1093/jn/132.8.2393S. PMID 12163699.](#) 1232
1233
1234
160. [Waterland RA, Jirtle RL \(August 2003\). "Transposable elements: targets for early nutritional effects on epigenetic gene regulation". Molecular and Cellular Biology. **23** \(15\): 5293–300. doi:10.1128/MCB.23.15.5293-5300.2003. PMC 165709. PMID 12861015.](#) 1235
1236
1237
161. [Dolinoy DC \(August 2008\). "The agouti mouse model: an epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome". Nutrition Reviews. **66** \(Suppl 1\): S7-11. doi:10.1111/j.1753-4887.2008.00056.x. PMC 2822875. PMID 18673496.](#) 1238
1239
1240
162. [Schulze KV, Bhatt A, Azamian MS, Sundgren NC, Zapata GE, Hernandez P, et al. \(November 2019\). "Aberrant DNA methylation as a diagnostic biomarker of diabetic embryopathy". Genetics in Medicine. **21**\(11\): 2453–2461. doi:10.1038/s41436-019-0516-z. PMID 30992551. S2CID 116880337.](#) 1241
1242
1243
163. [Callaway E \(1 December 2013\). "Fearful Memories Passed Down to Mouse Descendants: Genetic imprint from traumatic experiences carries through at least two generations". Nature Magazine – via Scientific American.](#) 1244
1245
1246
164. [Le Roux M \(13 December 2013\). "Mice can 'warn' sons, grandsons of dangers via sperm".](#) 1247
165. [Francis G \(October 2014\). "Too much success for recent groundbreaking epigenetic experiments". Genetics. **198** \(2\): 449–451. doi:10.1534/genetics.114.163998. PMC 4196602. PMID 25316784.](#) 1248
1249
1250
166. [Dias BG, Ressler KJ \(January 2014\). "Parental olfactory experience influences behavior and neural structure in subsequent generations". Nature Neuroscience. **17** \(1\): 89–96. doi:10.1038/nn.3594. PMC 3923835. PMID 24292232. \(see comment by Gonzalo Otazu\)](#) 1251
1252
1253
167. ["Epigenetics Paper Raises Questions".](#) 1254
168. [Hoekstra RF \(2000\). Evolution: an introduction. Oxford: Oxford University Press. p. 285. ISBN 978-0-19-854968-0.](#) 1255
1256
169. [Lamb MJ, Jablonka E \(2005\). Evolution in four dimensions: genetic, epigenetic, behavioral, and symbolic variation in the history of life. Cambridge, Massachusetts: MIT Press. ISBN 978-0-262-10107-3.](#) 1257
1258

170. [^](#) See also [Denis Noble](#): *The Music of Life*, esp pp. 93–98 and p. 48, where he cites Jablonka & Lamb and [Massimo Pigliucci](#)'s review of Jablonka and Lamb in *Nature* **435**, 565–566 (2 June 2005)
171. [^](#) Danchin É, Charmantier A, Champagne FA, Mesoudi A, Pujol B, Blanchet S (June 2011). "Beyond DNA: integrating inclusive inheritance into an extended theory of evolution". *Nature Reviews. Genetics*. **12** (7): 475–86. doi:10.1038/nrg3028. PMID 21681209. S2CID 8837202.
172. [^](#) Maynard Smith J (March 1990). "Models of a dual inheritance system". *Journal of Theoretical Biology*. **143**(1): 41–53. Bibcode:1990JThBi.143...41M. doi:10.1016/S0022-5193(05)80287-5. PMID 2359317.
173. [^](#) Lynch M (May 2007). "[The frailty of adaptive hypotheses for the origins of organismal complexity](#)". *Proceedings of the National Academy of Sciences of the United States of America*. **104** (Suppl 1): 8597–604. Bibcode:2007PNAS..104.8597L. doi:10.1073/pnas.0702207104. PMC 1876435. PMID 17494740.
174. [^](#) Dickins TE, Rahman Q (August 2012). "[The extended evolutionary synthesis and the role of soft inheritance in evolution](#)". *Proceedings. Biological Sciences*. **279** (1740): 2913–21. doi:10.1098/rspb.2012.0273. PMC 3385474. PMID 22593110.
175. [^](#) Rando OJ, Verstrepen KJ (February 2007). "[Timescales of genetic and epigenetic inheritance](#)". *Cell*. **128**(4): 655–68. doi:10.1016/j.cell.2007.01.023. PMID 17320504. S2CID 17964015.
176. [^](#) Lancaster AK, Masel J (September 2009). "[The evolution of reversible switches in the presence of irreversible mimics](#)". *Evolution; International Journal of Organic Evolution*. **63** (9): 2350–62. doi:10.1111/j.1558-5646.2009.00729.x. PMC 2770902. PMID 19486147.
177. [^](#) van der Graaf A, Wardenaar R, Neumann DA, Taudt A, Shaw RG, Jansen RC, et al. (May 2015). "[Rate, spectrum, and evolutionary dynamics of spontaneous epimutations](#)". *Proceedings of the National Academy of Sciences of the United States of America*. **112** (21): 6676–81. Bibcode:2015PNAS..112.6676V. doi:10.1073/pnas.1424254112. PMC 4450394. PMID 25964364.
178. [^](#) Griswold CK, Masel J (June 2009). "[Complex adaptations can drive the evolution of the capacitor \[PSI\], even with realistic rates of yeast sex](#)". *PLOS Genetics*. **5** (6): e1000517. doi:10.1371/journal.pgen.1000517. PMC 2686163. PMID 19521499.
179. [^](#) Jablonka E, Raz G (June 2009). "[Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution](#)" (PDF). *The Quarterly Review of Biology*. **84** (2): 131–76. CiteSeerX 10.1.1.617.6333. doi:10.1086/598822. PMID 19606595. S2CID 7233550. Archived from the original (PDF) on 15 July 2011. Retrieved 1 November 2017.
180. [^](#) Davies, Hazel (2008). *Do Butterflies Bite?: Fascinating Answers to Questions about Butterflies and Moths* (Animals Q&A). Rutgers University Press.
181. [^](#) Lewis ZA, Honda S, Khlafallah TK, Jeffress JK, Freitag M, Mohn F, et al. (March 2009). "[Relics of repeat-induced point mutation direct heterochromatin formation in Neurospora crassa](#)". *Genome Research*. **19** (3): 427–37. doi:10.1101/gr.086231.108. PMC 2661801. PMID 19092133.
182. [^](#) Jump up to: [^](#) Tost J (2008). *Epigenetics*. Norfolk, England: Caister Academic Press. ISBN 978-1-904455-23-3.
183. [^](#) Schadt EE, Banerjee O, Fang G, Feng Z, Wong WH, Zhang X, et al. (January 2013). "[Modeling kinetic rate variation in third generation DNA sequencing data to detect putative modifications to DNA bases](#)". *Genome Research*. **23** (1): 129–41. doi:10.1101/gr.136739.111. PMC 3530673. PMID 23093720.
184. [^](#) Davis BM, Chao MC, Waldor MK (April 2013). "[Entering the era of bacterial epigenomics with single molecule real time DNA sequencing](#)". *Current Opinion in Microbiology*. **16** (2): 192–8. doi:10.1016/j.mib.2013.01.011. PMC 3646917. PMID 23434113.

185. [^ Lluich-Senar M, Luong K, Lloréns-Rico V, Delgado J, Fang G, Spittle K, et al. \(2013\). Richardson PM \(ed.\). "Comprehensive methylome characterization of Mycoplasma genitalium and Mycoplasma pneumoniae at single-base resolution". PLOS Genetics. **9** \(1\): e1003191. doi:10.1371/journal.pgen.1003191. PMC 3536716. PMID 23300489.](#) 1302 1303 1304 1305
186. [^ Murray IA, Clark TA, Morgan RD, Boitano M, Anton BP, Luong K, et al. \(December 2012\). "The methylomes of six bacteria". Nucleic Acids Research. **40** \(22\): 11450–62. doi:10.1093/nar/gks891. PMC 3526280. PMID 23034806.](#) 1306 1307 1308
187. [^ Fang G, Munera D, Friedman DI, Mandlik A, Chao MC, Banerjee O, et al. \(December 2012\). "Genome-wide mapping of methylated adenine residues in pathogenic Escherichia coli using single-molecule real-time sequencing". Nature Biotechnology. **30** \(12\): 1232–9. doi:10.1038/nbt.2432. PMC 3879109. PMID 23138224.](#) 1309 1310 1311 1312
188. [^ Oliveira PH \(August 2021\). "Bacterial Epigenomics: Coming of Age". mSystems. **6** \(4\): e0074721. doi:10.1128/mSystems.00747-21. PMC 8407109. PMID 34402642. S2CID 237149441.](#) 1313 1314
189. [^ Casadesús J, Low D \(September 2006\). "Epigenetic gene regulation in the bacterial world". Microbiology and Molecular Biology Reviews. **70** \(3\): 830–56. doi:10.1128/MMBR.00016-06. PMC 1594586. PMID 16959970.](#) 1315 1316 1317
190. [^ Manso AS, Chai MH, Attack JM, Furi L, De Ste Croix M, Haigh R, et al. \(September 2014\). "A random six-phase switch regulates pneumococcal virulence via global epigenetic changes". Nature Communications. **5**: 5055. Bibcode:2014NatCo...5.5055M. doi:10.1038/ncomms6055. PMC 4190663. PMID 25268848.](#) 1318 1319 1320 1321
191. [^ Oliveira PH, Ribis JW, Garrett EM, Trzilova D, Kim A, Sekulovic O, et al. \(January 2020\). "Epigenomic characterization of Clostridioides difficile finds a conserved DNA methyltransferase that mediates sporulation and pathogenesis". Nature Microbiology. **5** \(1\): 166–180. doi:10.1038/s41564-019-0613-4. PMC 6925328. PMID 31768029.](#) 1322 1323 1324 1325
192. [^ Chahwan R, Wontakal SN, Roa S \(March 2011\). "The multidimensional nature of epigenetic information and its role in disease". Discovery Medicine. **11** \(58\): 233–43. PMID 21447282.](#) 1326 1327
193. [^ Jump up to: ^{a b c} Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, et al. \(July 2005\). "Epigenetic differences arise during the lifetime of monozygotic twins". Proceedings of the National Academy of Sciences of the United States of America. **102** \(30\): 10604–9. Bibcode:2005PNAS..10210604F. doi:10.1073/pnas.0500398102. PMC 1174919. PMID 16009939.](#) 1328 1329 1330 1331
194. [^ Jump up to: ^{a b} Kaminsky ZA, Tang T, Wang SC, Ptak C, Oh GH, Wong AH, et al. \(February 2009\). "DNA methylation profiles in monozygotic and dizygotic twins". Nature Genetics. **41** \(2\): 240–5. doi:10.1038/ng.286. PMID 19151718. S2CID 12688031.](#) 1332 1333 1334
195. [^ O'Connor A \(11 March 2008\). "The Claim: Identical Twins Have Identical DNA". New York Times. Retrieved 2 May 2010.](#) 1335 1336
196. [^ Ballestar E \(August 2010\). "Epigenetics lessons from twins: prospects for autoimmune disease". Clinical Reviews in Allergy & Immunology. **39** \(1\): 30–41. doi:10.1007/s12016-009-8168-4. PMID 19653134. S2CID 25040280.](#) 1337 1338 1339
197. [^ Wallace RG, Twomey LC, Custaud MA, Moyna N, Cummins PM, Mangone M, et al. \(2016\). "Potential Diagnostic and Prognostic Biomarkers of Epigenetic Drift within the Cardiovascular Compartment". BioMed Research International. **2016**: 2465763. doi:10.1155/2016/2465763. PMC 4749768. PMID 26942189.](#) 1340 1341 1342 1343
198. [^ Online Mendelian Inheritance in Man \(OMIM\): 105830](#) 1344

199. [^ Wood AJ, Oakey RJ \(November 2006\). "Genomic imprinting in mammals: emerging themes and established theories". PLOS Genetics. **2** \(11\): e147. doi:10.1371/journal.pgen.0020147. PMC 1657038. PMID 17121465.](#) 1345
1346
1347
200. [^ Knoll JH, Nicholls RD, Magenis RE, Graham JM, Lalande M, Latt SA \(February 1989\). "Angelman and Prader–Willi syndromes share a common chromosome 15 deletion but differ in parental origin of the deletion". American Journal of Medical Genetics. **32** \(2\): 285–90. doi:10.1002/ajmq.1320320235. PMID 2564739.](#) 1348
1349
1350
1351
201. [^ A person's paternal grandson is the son of a son of that person; a maternal grandson is the son of a daughter.](#) 1352
1353
202. [^ Pembrey ME, Bygren LO, Kaati G, Edvinsson S, Northstone K, Sjöström M, et al. \(February 2006\). "Sex-specific, male-line transgenerational responses in humans". European Journal of Human Genetics. **14** \(2\): 159–66. doi:10.1038/sj.ejhg.5201538. PMID 16391557. Robert Winston refers to this study in a "Lecture". Archived from the original on 23 May 2007.](#) 1354
1355
1356
1357
203. [^ "NOVA | Transcripts | Ghost in Your Genes". PBS. 16 October 2007. Retrieved 26 July 2012.](#) 1358
204. [^ Anderson SJ, Feye KM, Schmidt-McCormack GR, Malovic E, Mlynarczyk GS, Izbicki P, et al. \(May 2016\). "Off-Target drug effects resulting in altered gene expression events with epigenetic and "Quasi-Epigenetic" origins". Pharmacological Research. **107**: 229–233. doi:10.1016/j.phrs.2016.03.028. PMID 27025785.](#) 1359
1360
1361
1362
205. [^ Alavian-Ghavanini A, Rüegg J \(January 2018\). "Understanding Epigenetic Effects of Endocrine Disrupting Chemicals: From Mechanisms to Novel Test Methods". Basic & Clinical Pharmacology & Toxicology. **122** \(1\): 38–45. doi:10.1111/bcpt.12878. PMID 28842957.](#) 1363
1364
1365
206. [^ Coplan J, Chanatry ST, Rosenblum LA \(2017\). "Persistence of Early-Life Stress on the Epigenome: Nonhuman Primate Observations ☆". Reference Module in Neuroscience and Biobehavioral Psychology. doi:10.1016/B978-0-12-809324-5.02862-5. ISBN 9780128093245.](#) 1366
1367
1368
207. [^ Jump up to: ^a ^b Plomin R, DeFries JC, Knopik VS, Neiderhiser JM \(2017\). Behavioral Genetics \(Seventh ed.\). Worth Publishers. pp. 152–153. ISBN 978-1-4292-4215-8.](#) 1369
1370
208. [^ Heard E, Martienssen RA \(March 2014\). "Transgenerational epigenetic inheritance: myths and mechanisms". Cell. **157** \(1\): 95–109. doi:10.1016/j.cell.2014.02.045. PMC 4020004. PMID 24679529.](#) 1371
1372
209. [^ Robison AJ, Nestler EJ \(October 2011\). "Transcriptional and epigenetic mechanisms of addiction". Nature Reviews. Neuroscience. **12** \(11\): 623–637. doi:10.1038/nrn3111. PMC 3272277. PMID 21989194.](#) 1373
1374
1375
210. [^ Cheron J, Kerchoue d'Exaerde A \(August 2021\). "Drug addiction: from bench to bedside". Translational Psychiatry. **11** \(1\): 424. doi:10.1038/s41398-021-01542-0. PMC 8361217. PMID 34385417.](#) 1376
1377
1378
211. [^ Biliński P, Wojtyła A, Kapka-Skrzypczak L, Chwedorowicz R, Cyranka M, Studziński T \(2012\). "Epigenetic regulation in drug addiction". Annals of Agricultural and Environmental Medicine. **19** \(3\): 491–496. PMID 23020045.](#) 1379
1380
1381
212. [^ Vassoler FM, Sadri-Vakili G \(April 2014\). "Mechanisms of transgenerational inheritance of addictive-like behaviors". Neuroscience. **264**: 198–206. doi:10.1016/j.neuroscience.2013.07.064. PMC 3872494. PMID 23920159.](#) 1382
1383
1384
213. [^ Yuan TF, Li A, Sun X, Ouyang H, Campos C, Rocha NB, et al. \(November 2016\). "Transgenerational Inheritance of Paternal Neurobehavioral Phenotypes: Stress, Addiction, Ageing and Metabolism". Molecular](#) 1385
1386

- Neurobiology. **53** (9): 6367–6376. [doi:10.1007/s12035-015-9526-2](https://doi.org/10.1007/s12035-015-9526-2). [hdl:10400.22/7331](https://hdl.handle.net/10400.22/7331). PMID 26572641. S2CID 25694221.
214. [^] Chahwan R, Wontakal SN, Roa S (October 2010). "Crosstalk between genetic and epigenetic information through cytosine deamination". Trends in Genetics. **26** (10): 443–448. [doi:10.1016/j.tig.2010.07.005](https://doi.org/10.1016/j.tig.2010.07.005). PMID 20800313.
215. [^] Badal S, Her YF, Maher LJ (September 2015). "Nonantibiotic Effects of Fluoroquinolones in Mammalian Cells". The Journal of Biological Chemistry. **290** (36): 22287–22297. [doi:10.1074/jbc.M115.671222](https://doi.org/10.1074/jbc.M115.671222). PMC 4571980. PMID 26205818.
216. [^] Mezentsseva NV, Yang J, Kaur K, Iaffaldano G, Rémond MC, Eisenberg CA, et al. (February 2013). "The histone methyltransferase inhibitor BIX01294 enhances the cardiac potential of bone marrow cells". Stem Cells and Development. **22** (4): 654–667. [doi:10.1089/scd.2012.0181](https://doi.org/10.1089/scd.2012.0181). PMC 3564468. PMID 22994322.
217. [^] Yang J, Kaur K, Ong LL, Eisenberg CA, Eisenberg LM (2015). "Inhibition of G9a Histone Methyltransferase Converts Bone Marrow Mesenchymal Stem Cells to Cardiac Competent Progenitors". Stem Cells International. **2015**: 270428. [doi:10.1155/2015/270428](https://doi.org/10.1155/2015/270428). PMC 4454756. PMID 26089912.
218. [^] Müller S, Sindikubwabo F, Cañeque T, Lafon A, Versini A, Lombard B, et al. (October 2020). "CD44 regulates epigenetic plasticity by mediating iron endocytosis". Nature Chemistry. **12** (10): 929–938. Bibcode:2020NatCh..12..929M. [doi:10.1038/s41557-020-0513-5](https://doi.org/10.1038/s41557-020-0513-5). PMC 7612580. PMID 32747755.
219. [^] Solier S, Müller S, Cañeque T, Versini A, Mansart A, Sindikubwabo F, et al. (May 2023). "A druggable copper-signalling pathway that drives inflammation". Nature. **617** (7960): 386–394. Bibcode:2023Natur.617..386S. [doi:10.1038/s41586-023-06017-4](https://doi.org/10.1038/s41586-023-06017-4). PMC 10131557. PMID 37100912.
220. [^] Liu N, Pan T (January 2015). "RNA epigenetics". Translational Research. **165** (1): 28–35. [doi:10.1016/j.trsl.2014.04.003](https://doi.org/10.1016/j.trsl.2014.04.003). PMC 4190089. PMID 24768686.
221. [^] Rong D, Sun G, Wu F, Cheng Y, Sun G, Jiang W, et al. (September 2021). "Epigenetics: Roles and therapeutic implications of non-coding RNA modifications in human cancers". Molecular Therapy. Nucleic Acids. **25**: 67–82. [doi:10.1016/j.omtn.2021.04.021](https://doi.org/10.1016/j.omtn.2021.04.021). PMC 8217334. PMID 34188972. S2CID 235558945.
222. [^] Shin H, Choi WL, Lim JY, Huh JH (March 2022). "Epigenome editing: targeted manipulation of epigenetic modifications in plants". Genes & Genomics. **44** (3): 307–315. [doi:10.1007/s13258-021-01199-5](https://doi.org/10.1007/s13258-021-01199-5). PMID 35000141. S2CID 245848779.
223. [^] Jump up to: ^a^b^c^d^e^f^g Hawe JS, Wilson R, Schmid KT, Zhou L, Lakshmanan LN, Lehne BC, et al. (January 2022). "Genetic variation influencing DNA methylation provides insights into molecular mechanisms regulating genomic function". Nature Genetics. **54** (1): 18–29. [doi:10.1038/s41588-021-00969-x](https://doi.org/10.1038/s41588-021-00969-x). PMC 7617265. PMID 34980917. S2CID 245654240. Archived from the original on 29 October 2022. Retrieved 20 January 2023.
224. [^] Lee ST, Feng M, Wei Y, Li Z, Qiao Y, Guan P, et al. (July 2013). "Protein tyrosine phosphatase UBASH3B is overexpressed in triple-negative breast cancer and promotes invasion and metastasis". Proceedings of the National Academy of Sciences of the United States of America. **110** (27): 11121–11126. Bibcode:2013PNAS..11011121L. [doi:10.1073/pnas.1300873110](https://doi.org/10.1073/pnas.1300873110). PMC 3704014. PMID 23784775.
225. [^] Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. (October 2018). "Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of

- [European ancestry". Human Molecular Genetics. 27 \(20\): 3641–3649. doi:10.1093/hmg/ddy271. PMC 6488973. PMID 30124842.](#)
226. [^ Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, et al. \(January 2019\). "Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry". Human Molecular Genetics. 28 \(1\): 166–174. doi:10.1093/hmg/ddy327. PMC 6298238. PMID 30239722.](#)
227. [^ Zhu Z, Guo Y, Shi H, Liu CL, Panganiban RA, Chung W, et al. \(February 2020\). "Shared genetic and experimental links between obesity-related traits and asthma subtypes in UK Biobank". The Journal of Allergy and Clinical Immunology. 145 \(2\): 537–549. doi:10.1016/j.jaci.2019.09.035. PMC 7010560. PMID 31669095.](#)
228. [^ Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G, et al. \(March 2020\). "Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: A multivariable Mendelian randomisation analysis". PLOS Medicine. 17 \(3\): e1003062. doi:10.1371/journal.pmed.1003062. PMC 7089422. PMID 32203549.](#)
229. [^ Konieczna J, Sánchez J, Palou M, Picó C, Palou A \(March 2015\). "Blood cell transcriptomic-based early biomarkers of adverse programming effects of gestational calorie restriction and their reversibility by leptin supplementation". Scientific Reports. 5 \(1\): 9088. Bibcode:2015NatSR...5.9088K. doi:10.1038/srep09088. PMC 4357898. PMID 25766068.](#)
230. [^ Okada Y \(November 2014\). "From the era of genome analysis to the era of genomic drug discovery: a pioneering example of rheumatoid arthritis". Clinical Genetics. 86 \(5\): 432–440. doi:10.1111/cge.12465. PMID 25060537. S2CID 8499325.](#)
231. [^ He Z, Zhang R, Jiang F, Zhang H, Zhao A, Xu B, et al. \(August 2018\). "FADS1-FADS2 genetic polymorphisms are associated with fatty acid metabolism through changes in DNA methylation and gene expression". Clinical Epigenetics. 10 \(1\): 113. doi:10.1186/s13148-018-0545-5. PMC 6114248. PMID 30157936.](#)
232. [^ Guan W, Steffen BT, Lemaitre RN, Wu JH, Tanaka T, Manichaikul A, et al. \(June 2014\). "Genome-wide association study of plasma N6 polyunsaturated fatty acids within the cohorts for heart and aging research in genomic epidemiology consortium". Circulation: Cardiovascular Genetics. 7 \(3\): 321–331. doi:10.1161/circgenetics.113.000208. PMC 4123862. PMID 24823311.](#)
233. [^ Shin SY, Fauman EB, Petersen AK, Krumsiek J, Santos R, Huang J, et al. \(June 2014\). "An atlas of genetic influences on human blood metabolites". Nature Genetics. 46 \(6\): 543–550. doi:10.1038/ng.2982. PMC 4064254. PMID 24816252.](#)
234. [^ Astle WJ, UK Blood Trait GWAS Team, Cambridge BLUEPRINT epigenome \(2 December 2016\). "A GWAS of 170,000 Individuals Identifies Thousands of Alleles Perturbing Blood Cell Traits, Many of Which Are in Super Enhancers Setting Cell Identity". Blood. 128 \(22\): 2652. doi:10.1182/blood.v128.22.2652.2652. ISSN 0006-4971.](#)
235. [^ Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, et al. \(November 2019\). "PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations". Bioinformatics. 35 \(22\): 4851–4853. doi:10.1093/bioinformatics/btz469. PMC 6853652. PMID 31233103.](#)
236. [^ Gorski D \(4 February 2013\). "Epigenetics: It doesn't mean what quacks think it means". Science-Based Medicine.](#)

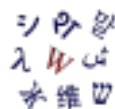
Further reading

[edit]

- Haque FN, Gottesman II, Wong AH (May 2009). "Not really identical: epigenetic differences in monozygotic twins and implications for twin studies in psychiatry". *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*. **151C** (2): 136–41. doi:10.1002/ajmg.c.30206. PMID 19378334. S2CID 205327825.
- "What is Epigenetics?". Centers for Disease Control and Prevention. 15 August 2022. Retrieved 11 September 2023.

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- [Canadian Epigenetics, Environment and Health Research Consortium \(CEEHRC\)](#)
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